Cancer of Unknown Primary (CUP) Consortium

OUTLINE

Between 3-10% of all worldwide diagnosed cancers, its primary tissue of origin cannot be determined, which has a direct impact on the outcome of such patients. In such scenario, where the metastases are clinically manifested, but the primary tumoration originating them is unknown, the physician diagnoses those patients as Cancer of Unknown Primary (CUP). Clinically, CUP is defined as a histologically confirmed malignant tumor, incompatible with a primary neoplasm in the biopsy area, whose origin is not clear after performing a thorough clinical history, complete physical examination, and basic complementary studies. Nevertheless, this definition is not an international standard in terms of diagnostic codes, as depending on the institution and country this varies. As a result of this challenging situation, just one of every four (25%) CUP cases, complete immunohistochemistry tests or post-mortem examination, reveals the primary tumor, nevertheless, in the majority of CUPs (75%) their primary tumor cannot be identified.

Epidemiological studies involving CUP cases are scarce and difficult to compare among them, mainly due to the aforementioned different inclusion criteria. The available studies, performed mainly on northern European countries, Australia and USA, covers half century historical data (1960 – 2010), highlighting the distinctive trends of this disease. These studies have revealed an increasing CUP incidence over the 1960-1980 period, reaching up to 16.0 per 100.000 inhabitants. Interestingly, differing on the starting year in each of the analysed populations, a clear reduction in the incidence has been observed, with nowadays incidence of 8.0 per 100.000 inhabitants. The reasons for such reduction are postulated to be the advances in diagnostic methods at a biological, radiological and pathological approaches, however, it might also be a consequence of insufficient diagnostic inquiry, a phenomena documented on the USA population.

Due to the fact that conventional diagnostic techniques (immunohistochemistry, imaging,..) usually fail to identify the tissue of origin, molecular profiling techniques were introduced for cancer of unknown primary diagnosis in 2005 as a new approach to analyzed quantitative and simultaneously the molecular profile of bigger panels of genes characteristically and differentially altered between the different tumor types. Different approaches have been taken, such as RNA expression, microRNA detection, and DNA methylation. Those strategies enabled the prediction of the tissue of origin in cancer of unknown primary, by the comparison of its molecular profile with a set of primary / metastatic tumors of known origin. When comparing the validation of all available molecular diagnostic solutions for CUP, DNA methylation-based prediction have shown more confidence than platforms based on gene expression or microRNA.

Based in the DNA methylation capacity to discriminate among different tissue types, we have developed a diagnostic tool with enough robustness to be applied in the clinical practice. The effectiveness of methylation patterns as predictor of tumor origin was demonstrated using a cohort of 216 CUP cases internationally collected.

Studies performed in cancer of unknown primary cohorts have preliminary shown that the administration of a site-specific treatment in concordance with the molecular-predicted tissue of origin, entail a benefit in terms of survival rates in patients with CUP. However, further prospective clinical trials are necessary to elucidate the impact of specific site tailored therapies in survival improvement. This will lead to the avoidance of inefficient therapies and a decrease in the arising health costs; two aspects of significant relevance for metastatic lesion of unknown origin, as these cannot be classified into a particular neoplasia and consequently have to be treated in an empiric manner, resulting in the peculiar poor survival rates in cancer of unknown primary.

AIM OF THE PROPOSAL

Following the high standards of the previous TCGA projects, the current proposal aims to provide a comprehensive genomic landscape of the Cancer of Unknown Primary that includes exome sequencing, copy-number variation, DNA methylation, RNA-sequencing transcriptome and bioinformatic analyses of 500 cases of clinically well characterized CUP cases to improve the unmet medical need.

Initially, extensive characterization of the 216 cases used in the aforementioned study of methylation as an effective predictor of tumor origin is envisioned. While this characterization is ongoing the additional 300 cases will be collected by the clinical members of the consortium (see below).

Contribution to the consortium would be as follows:

Clinical Collaborators: Identification and collection of cases, participation in the Analysis Working Group to review the data and write the manuscript(s).

Josep Carreras Research Institute: Perform DNA methylation analysis in all the cases collected, participation in the Analysis Working Group to review the data and write the manuscript(s).

National Cancer Institute (USA): General coordination of the consortium, sample processing to generate analytes, characterization of cases (Whole Exome Sequencing, Whole Genome Sequencing, Total RNA sequencing), participation in the Analysis Working Group to review the data and write the manuscript(s).

PROPOSED CLINICAL MEMBERS/COLLABORATORS

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**The proposal is fully open to invite other experts following any suggestion of the evaluating panel.*