

# MOLECULAR ANALYSIS OF THE METASTATIC PROCESS IN CHILDHOOD TUMORS

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## 1. Summary of the project

Developmental tumors (DTs) are very aggressive and highly metastatic. Approximately one third of patients have metastases at the time of diagnosis, with the lungs and bone marrow being the most common sites. The 5-year survival of patients with metastasis ranges from 20% to 45% depending on location (lungs and bone/bone marrow respectively), compared to 60-70% for those with localized disease. The lack of knowledge about the molecular mechanisms that regulate the metastatic process is the main cause that explains the lack of clinical therapeutic efficacy in these patients. Therefore, with the aim of finding new biomarkers for diagnosis and new therapeutic targets, it is mandatory to have a wider knowledge of the key regulators of the metastatic process. In this proposal we have obtained a genetic and epigenetic signature of the metastases specific to these DTs. To achieve this, we used orthotopic models developed in our laboratories, which recapitulate all the steps a cell goes through to reach its most frequent site of metastasis. The obtained signature is being validated in different cohorts of patients. The pharmacological interruption of the possible routes obtained from this complete and validated signature will allow us to develop new therapeutic strategies for the treatment of patients with a high metastatic risk by preventing their appearance or treating already existing metastases.

## 2. Results

Thanks to the completion of this project, we discovered that the tumor cells characteristic of a DT recapitulate their progression in the patient from which they were obtained in the model of spontaneous metastases that was developed. Thus, both models have developed lymphatic and blood dissemination. Despite following similar processes, metastatic signatures are dependent on the tumor of origin and not process-dependent. The transcriptomic profile was the easiest to obtain and is the one that gave us most information in both cases. However, we have obtained specific profiles that define the metastases of these tumors both at the transcriptomic and epigenomic level. Both in rhabdomyosarcoma (RMS) and in the case of neuroblastoma (NB), we have discovered two new biomarkers that stand out as new potential therapeutic targets as anti-metastatic therapy.

## 3. Relevance with possible future implications

The development of new, more efficient and safer therapies for the treatment of primary tumors is one of the main objectives, not only of the scientific and clinical community, but also of society in general and associations of families of children with cancer in particular. A major concern in pediatric cancer research is that therapies designed for adults are being administered. But children are not small adults and the molecular mechanisms involved in tumorigenesis are different. Therefore, therapies directed against childhood cancer should be directed against specific characteristics of this type of tumor.

In this study we present a multi-omic approach to investigate the molecular mechanisms involved in the progression and metastasis of certain DTs. By combining genetic and epigenetic techniques we have managed to identify signaling pathways and specific targets that could be important for the progression of this disease. Remarkably, this is the first multi-omics approach performed in a spontaneous metastasis model generated from patient samples. In this work we demonstrate the involvement of different genes in the metastatic process and therefore, their use as possible prognostic biomarkers and/or as potential therapeutic targets. The results obtained will open new possibilities in the design of innovative tools for the treatment of these diseases. These new strategies can mean a reduction in the harmful non-specific effects of chemotherapy and at the same time result in an improvement in the survival and quality of life of the patients.

The results obtained from the research carried out with La Fundació La Marató de TV3 will serve as a basis for continuing the project with the evaluation of the potential use of a specific inhibitor of the identified biomarker, as a proof of concept for the development of new anti-metastasis therapies.

## 4. Bibliography

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