Please, allow me to introduce you to a rare but exceptionally aggressive type of brain tumor named Atypical Teratoid Rhabdoid Tumor (AT/RT).

AT/RT is an embryonal tumor that tends to occur in children younger than 2 years of age and most frequently arises in the central nervous system (CNS), but can also develop in the kidney, soft tissue, liver and other locations. When it arises outside the CNS, it receives the generic name of Malignant Rhabdoid Tumor (MRT) or simply Rhabdoid tumor.

Rhabdoid tumors (AT/RT or MRT) are among the most aggressive and lethal malignancies in pediatrics and this diagnosis mean a rapid progression to death in the absolute majority of cases. The fact that 70% of children have already tumor spread at the time of the diagnosis and a time to relapse of only 10 months illustrate its dramatic clinical course.
Children present extremely poor outcome despite being treated with surgery, radiation therapy and a highly toxic combination of chemotherapy agents. Current multimodal therapy leads to major deficits in the developing brain and drug toxicity results in a large range of side effects. Aiming to achieve a longer survival with fewer side effects and to provide hope to the parents of children that develop these unresponsive tumors, we have been focusing our efforts to find more effective and less toxic therapeutic options for Rhabdoid tumors. Our efforts include two fronts of action: genetic studies and the development of a new animal model.

Our genetic studies are based on the fact that Rhabdoid tumors are characterized by mutations that inactivate the tumor suppressor gene INI1 (also known as SMARCB1, hSNF5 and BAF47). A recent study revealed that approximately one-third of patients with AT/RT have an underlying genetic predisposition due to a germline INI1 alteration. However, at this point, we don't have a clear knowledge about at what level germline mutations reflect in the location, age or prognosis of a Rhabdoid tumor. In fact, we still don't know what triggers the mutation and consequent tumor development. These are things that we are trying to understand.

In addition, based on the observation of isolated cases of Rhabdoid tumors that present long-survival not related to age, clinical stage, radiation therapy or extension of surgical excision, we hypothesized that a distinctive genetic background allows these patients to present longer survival than ordinary Rhabdoid tumors. To understand this phenomenon and learn how to successfully improve survival of all other children, we are currently working on the genetic characterization of AT/RT and MRT families. With an extensive genetic evaluation we hope to find factors that not only act in tumor formation, location and clinical course but also to disclose new potential therapeutic targets.

We have been privileged to be contacted by numerous families worldwide volunteering to participate in this family study. This overwhelming support and participation is very important as a bigger number of families increase our chances to meaningful and statistically significant findings give the rarity of this condition.

Since large clinical trials that could test new therapeutic agents and address critical biological questions are difficult to conduct due to the low incidence of this type of cancer, high throughput preclinical testing with a suitable animal model is critical for identifying efficacious treatments for

Rhabdoid tumors. In response to this need, we are working in developing a new animal model for Rhabdoid tumors that is particularly amenable to performing high throughput drug screens for the identification of new therapeutic intervention. Our model has the overwhelming potential to improve both the clinical care and the prognosis of children suffering with Rhabdoid tumors.

Together with Dr. Tadanori Tomita, head of the Division of pediatric Neurosurgery at Ann and Robert H. Lurie Children's Hospital of Chicago, we have launched iSTAR – an Initiative for the Study and Translational AT/RT Research (http://www.luriechildrensresearch.org/iSTAR_AT_RT/). iSTAR was created to inform families about our studies, raise awareness and get support from the community, allowing us to move forward with our research in this very necessary but underfunded area. We are confident that progress on the Rhabdoid tumor knowledge and treatment will beneficiate not only children suffering for this invariably lethal disease but will teach us lessons on how to beat other aggressive pediatric solid tumors as well.

I would like to thank Dr. Musella, for the opportunity to share with you our efforts and concerns and to raise awareness against AT/RT.

Sincerely yours,

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