

October 8, 2007

Summary of the 1<sup>st</sup> International Costello Syndrome Research Symposium  
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**WHAT, WHERE, WHEN:**

The family focused activities of the 6<sup>th</sup> Bi-Annual Costello Conference took place Thursday, Friday and Sunday at Doernbecher Children's Hospital in Portland, Oregon. On Saturday, July 21, 2007, the 1<sup>st</sup> International Costello Syndrome Research Symposium was held, sponsored by the NIH, Office of Rare Disease and the National Institute of Child Health and Human Development, among other supporters. Please refer to the meeting agenda for a full listing of participants, sponsors and abstracts.

**PURPOSE:**

The Research Symposium was designed to bring interested researchers to educate them about Costello syndrome, and promote discussion about research with particular attention to possible drug therapy.

**INTRODUCTION:**

What better way for the speakers and guests to learn about Costello syndrome than to have individuals speak about themselves as "self advocates". This was done with stunning success in the form of videotaped presentations prepared by Kristin Carillo, Erin Hefner, Laure Messier and Jill Taylor. Everyone who viewed these videos had a deeper sense of what it meant to live with Costello syndrome, not to mention a personal affection for the gracious individuals themselves. [We encourage everyone to view these, at the the Costello Kids website.]

**SESSION 1: MOLECULAR RESEARCH**

Dr. Kate Rauen presented the details of the RAS- MAPK pathway, highlighting the close biological interaction of the gene products affected by mutations in Costello, CFC, Noonan and other closely related syndromes. Increased signaling through the RAS-MAPK pathway is the common biologic mechanism in these related syndromes. The understanding of the pathway helps researchers delineate the respective similarities and differences between the syndromes.

Dr. Yoko Aoki described in detail *HRAS*, the gene which causes Costello syndrome. *HRAS* has long been known as an oncogene, and much of what we know about the protein function was learned through cancer research.

Dr. Karen Gripp reported on the incidence of the more common Costello syndrome causing mutations, e.g. G12S, and some of the rare changes in *HRAS*. It is likely that some mutations have a stronger effect on the RAS-MAPK pathway than others, and may therefore cause more severe findings; however, not many patients with rare mutations have been identified at this time.

**SESSION 2: CLINICAL**

Dr. Virginia Proud provided an overview over the delineation of Costello syndrome.

Dr. Judith Allanson and Peter Hammond presented information on the facial features of Costello, CFC and Noonan syndrome, and novel data from 3D computer mapping of facial images. Dr. Hammond has been able to show a clustering of the data for specific syndromes, and may be able to infer a possible diagnosis based on his data analysis.

Dr. Marie-Ange Delrue reviewed the central nervous system problems in Costello syndrome, especially: Chiari 1 malformation, an abnormality at the base of the skull and brain, which remains the most common problem requiring surgical intervention.

Dr. Marnie Axelrad shared her results from cognitive testing studies performed at two previous Costello meetings, her work continued at the 2007 meeting. She found that despite overall cognitive delay, fluid reasoning is an area of relative strength, whereas expressive language is an area of particular weakness among Costello patients.

Dr. Angela Lin presented her data on the cardiac involvement which is present in over 80% of Costello patients. Hypertrophic cardiomyopathy occurs in almost two-thirds. Preliminary data does not show a causal relationship to the use of growth hormone, although this needs to be interpreted very cautiously. Chaotic or multifocal tachycardia, a type of fast heart beat, remains a distinguishing finding seen in Costello, but not in CFC or Noonan syndrome.

Dr. Daniel Doyle reviewed information on growth hormone deficiency, which is seen in almost half of all Costello patients.

Dr. Bronwyn Kerr reviewed malignant tumors in Costello syndrome and confirmed the previously reported 17% risk for developing any kind of malignant tumor. Upon closer analysis stratified by specific *HRAS* mutation, there is a suggestion that the tumor risk may be higher for patients with some of the rare mutations; however, the total number of patients is too small to derive statistically meaningful data.

### SESSION 3: TREATMENT

This discussion about possible drug therapy is based on the information about the RAS-MAPK pathway, elucidated in great detail through cancer research. The pathway is known to be overly active in many types of malignancy, and was thus the target of different pharmaceutical compounds.

Dr. Frank McCormick reviewed some of the drugs used to inhibit the MAPK pathway. MEK inhibitors may be promising not only for use in Costello syndrome, but also in CFC syndrome, and possibly other disorders within the pathway. In contrast, farnesyl transferase inhibitors (FTIs) failed in previous experiments because they were used to target changes in *KRAS*. Based on its biochemical properties, *HRAS* is expected to be sensitive to farnesyl transferase inhibitors, and these compounds may thus prove to be effective for patients with Costello syndrome.

Dr. Mark Kieran discussed the farnesyl transferase inhibitors in more detail, and outlined the ongoing study in patients with a completely different genetic disorder, progeria.

Dr. Silva proposed a different treatment approach, whose work focuses on the central nervous system and its function in the mouse model for neurofibromatosis (NF), another MAPK pathway disorder. Lovastatin, a medication used in people with elevated cholesterol level, is a known inhibitor of the MAPK activity. Dr. Silva reports that lovastatin had a positive effect on the attention span and spatial learning in NF mice.

Dr. Alek Hinek provided an overview over his work related to chondroitin sulfate metabolism in patients with Costello syndrome and suggested that Costello syndrome fibroblasts may show a temperature dependent phenotype.

Dr. Tan Nguyen described the possible role the FDA could play in the planning and review of drug trials.

In summary, more than one treatment modalities may show promise for the medical therapy of Costello patients. However, it is a long way from the concept of drug therapy to its application in human patients. It became clear that a well planned, collaborative effort is required to collect meaningful information. Early steps may include the development of mouse models, collaboration among researchers, and fund raising for a large study. We did not have time to have a formal panel discussion at the meeting, but there was a sense among the researchers that therapeutics could be considered in order to improve the life of patients with Costello syndrome.

Addendum: This summary was prepared specifically for the parents' website. There is also a summary being submitted for publication in the American Journal of Medical Genetics. When published, we will try to make this available to you, too.