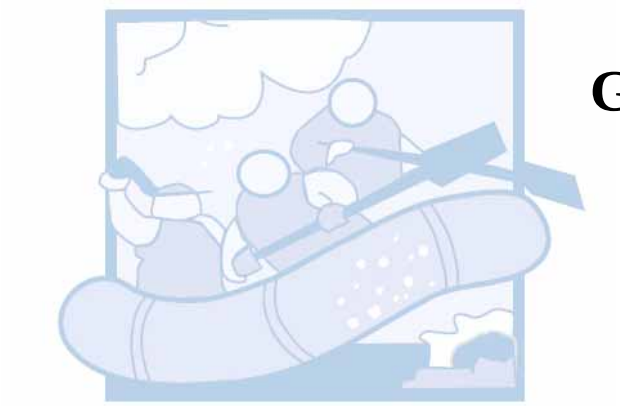

Group Leader Plan of Action for Priority Project I:

Pediatric GIST

Date: December 21, 2005

Group Leader: Cristina Antonescu
Sloan Kettering Institute for Cancer Research
1275 York Avenue
New York, NY 10021

Major Aim:	Identify the Molecular Mechanisms and Potential Drug Targets for Pediatric GIST.

	Project Components	**Investigators**	**% Effort**
I-1	Identifying Novel Therapeutic Targets in Pediatric GIST based on Gene Expression Array Profiling	Antonescu	100
I-2	Comparative Gene Expression Profiling of WT Adult and Pediatric GISTs.		
			100%

Background and Significance

GISTs are mesenchymal tumors that typically present in adults over the age of 40 years and are commonly associated with activating mutations in *KIT* or *PDGFRA* tyrosine kinase genes. GISTs in pediatric and younger patients are rare and not well characterized. Our previous work suggested that GISTs in children represent a distinct clinicopathologic and molecular subset, with predilection for females, multifocal gastric location, and wild-type *KIT/PDGFRA* genotype. Other distinct features for the pediatric subset included a high propensity for regional lymph node metastasis and local recurrence to the gastric stump. In spite of the multinodular and multifocal gross appearance within the stomach, none of the tumors studied showed evidence of interstitial cell of Cajal (ICC) hyperplasia. This latter finding is commonly seen in the familial GIST syndrome, as well as in GIST associated with neurofibromatosis type I. GISTs associated with Carney's triad typically occur in a younger age group and female sex predominance, and include one or two additional tumors, such as extra-adrenal paraganglioma and pulmonary chondroma. The cases reported to date within the spectrum of Carney's triad bear a close resemblance to the sporadic pediatric GISTs, which are typically located in the stomach, multifocal, epithelioid, and often associated with regional lymph

node metastases. Moreover, the relatively long survival of patients with Carney's triad, even in the presence of lymph node or liver metastatic disease, closely resembles the biology of the sporadic pediatric GISTs. As observed in our pediatric patients, the multiple gastric tumors seen with Carney's triad patients also required multiple gastric operations, which ended with total gastrectomy for their eradication. Like patients with Carney's triad there is no evidence of familial disease identified in "sporadic" pediatric GISTs, therefore it is possible that some of the latter cases represent a form fruste of this syndrome.

Although in our previous data all 6 pediatric patients for whom clinical follow up was available developed recurrence (4 in the liver, 4 in the peritoneum, and 2 in both sites), 5 are still alive with disease after a mean follow-up of 85.2 months. In spite of a high recurrence rate, both in the liver and elsewhere within the abdomen, the clinical behavior of pediatric GIST appears more indolent, even in the absence of imatinib therapy, as compared with adult GISTs. This indolent clinical course suggests a different biology of pediatric GISTs, as compared with their adult counterparts. Of the 2 pediatric patients that were treated with imatinib for their recurrent disease, one had no response and the other had stable disease after 12 months treatment. More data on pediatric patients will be necessary to determine if imatinib achieves a comparable partial response or stable disease in over 75% of patients as it does in adults.

In contrast GISTs in young adults represent a more heterogeneous group, including cases resembling either pediatric or older adult-type tumors. Of the 10 young adults GISTs studied in our Institution, 5 occurred in the small bowel and had spindle cell morphology, and 1 showed lymph node metastasis. *KIT* mutations were identified in 7 cases, 4 in exon 11 and 3 in exon 9. Seven patients developed recurrence and at last follow-up 2 patients have died of disease.

In summary, pediatric GISTs represent a distinct subset of this rare sarcoma, with strong predominance for females, multifocal gastric location, indolent biology, and a wild-type *KIT*/*PDGFRA* genotype.

Project I-1	**Identifying Novel Therapeutic Targets in Pediatric GIST based on Gene Expression Array Profiling**
Principal Investigator	Cristina Antonescu
Sponsoring Institution	Sloan Kettering Institute for Cancer Research 1274 York Avenue New York, NY 10021
Goals	
Long Term	After appropriate validation, candidate genes will be selected for sequencing for possible activating mutations.
Short Term	Validation of candidate genes identified on expression analysis by qRT-PCR and/or IHC.

Specific Aims:

Investigate potential candidate genes and therapeutic targets for possible oncogenic mutations based on their expression on the transcriptional microarray profiling. Our preliminary results on 7 gastric tumor samples from 2 children and 2 young adults, using a U133A Affymetrix platform (22,000 genes), identified a number of differentially expressed genes as compared to the adult population. High expression of *PHKA1, IGF1R, FZD2, NLGN4,* and *ANK3* were seen in the pediatric versus older adult cases. This distinct gene expression profile suggests avenues for investigation of pathogenesis and potential therapeutic strategies.

Project I- 2	**Comparative Gene Expression Profiling of WT Adult and Pediatric GISTs.**
Principal Investigator	Cristina Antonescu
Sponsoring Institution	Sloan Kettering Institute for Cancer Research 1274 York Avenue New York, NY 10021
Goals	
Long Term	Candidate genes validation by qRT-PCR and/or immunohistochemistry, tested for their activated biochemical profile or oncogenic mutations by sequencing.
Short Term	RNA extraction, Affymetrix U133A chip hybridization and data analysis of additional pediatric and adult WT GISTs.

Specific Aims:

Certain clinicopathologic features of pediatric GIST, such as predilection for girls, multifocal gastric location and wild-type genotype, suggest a distinct biology for this subset, as compared with the adult counterpart. The less than favorable imatinib response in adult wild-type GIST patients, have so far impacted the enthusiasm in treating children with imatinib, either in metastatic/ recurrent or adjuvant settings. As a result, data on the imatinib response in pediatric GIST patients is lacking and anecdotal evidence is conflicting. An important question to be answered in this proposal is if in fact wild-type pediatric GIST represents a molecularly distinct group as compared with the wild-type adult GIST subset. We will use transcriptional expression platform to compare our group of wild-type adult GIST tumors with the pediatric cases. Our hypothesis is that pediatric GIST are indeed distinct at the genomic level and therefore in-depth knowledge of their expression signature might resolve the dispute over its intrinsic resistance to imatinib, as well as identifying novel therapeutic targets.