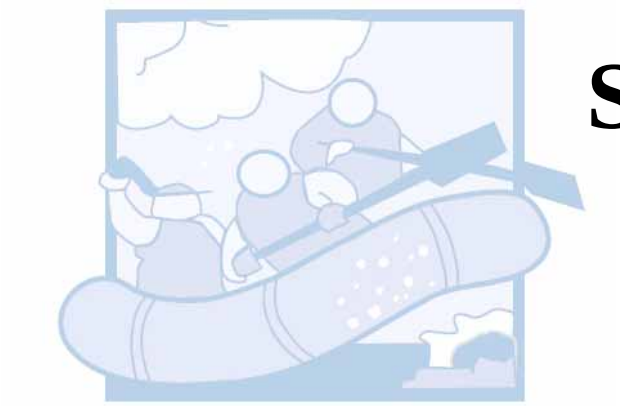

Summary of Priority Projects

Imatinib Resistance Mechanisms

- Dr. Jonathan Fletcher

The research program implemented by the Life Raft Group will support highly integrated research that characterizes mechanisms by which gastrointestinal stromal tumors (GISTs) develop resistance to therapeutic KIT inhibition. The studies will evaluate therapeutic modalities that can be combined with imatinib treatment to improve response duration and approach a cure, for patients with GIST. The studies will be conducted by investigators with a leadership role in GIST research and whose laboratories are primarily focused on GIST science. Each of the investigators is committed to working together, integrating research results, and identifying promising approaches that will enhance the cornerstone role of imatinib therapy for GIST patients.

The scientific themes have been organized into ten priority research programs including two highly annotated GIST tissue banks to support the projects.

Priority Project A – Peter Besmer, Memorial Sloan-Kettering Cancer Center.
Oncogenic KIT Signaling Mechanisms

Peter Besmer is one of the co-discoverers of the KIT protein and he has studied KIT oncogenic mechanisms for more than fifteen years. He is superbly positioned to orchestrate Project A with objectives of understanding how activated KIT molecules translate their abnormal activity into GIST cell proliferation and survival. These will be performed in human GISTs, in cells transformed by mutant KIT oncogenes, and in transgenic mouse GIST models. These studies will inform us of critical pathway attack points that can be paired with imatinib to develop therapeutic synergies.

Priority Project B – Matt van de Rijn, Stanford University
KIT/PDGFRA wildtype GISTs

Dr. van de Rijn is expert in gene and protein profiling in GIST and he is, therefore, well qualified to coordinate Project B. This project seeks to identify alternative oncogenic mechanisms in GISTs lacking KIT or PDGFRA mutations. The alternate oncogenic mechanisms will be identified by profiling the genes and proteins expressed in these GISTs. These studies will identify "escape" mechanisms by which GISTs can activate proteins that are not susceptible to imatinib inhibition. The investigators will

evaluate the hypothesis that such mechanisms can then be targeted to develop therapeutic synergies with imatinib.

Priority Project C – Christopher Corless and Michael Heinrich, Oregon Health Sciences University

Primary Imatinib Resistance

Drs. Corless and Heinrich are leaders in genomic evaluation of KIT mutations and imatinib response mechanisms in GISTs. This project evaluates the mechanisms accounting for lack of clinical response to imatinib in a subset of GIST patients. These studies will then determine whether novel kinase inhibitor drugs are better suited for inhibiting the particular KIT (or PDGFRA) mutations that show primary resistance to imatinib. In addition, proteinic methods will be used to determine why the subset of GISTs with exon 9 KIT mutations have an unsatisfactory response to imatinib.

Priority Project D – Maria Debiec-Rychter, Catholic University of Leuven, Belgium

Stable Disease

Dr. Debiec-Rychter is a leader in GIST research in the European community, and her group has extensive experience in the research of mechanisms of imatinib response and resistance. Project D evaluates stable disease in patients who initially have a therapeutic response to imatinib, but in whom the clinical response then plateaus, leaving the patients with substantial amounts of radiographically evident tumor. The project will determine why subsets of GIST cells continue to survive in the face of imatinib therapy, even though the overall GIST lesion was responsive to imatinib. In addition, these studies will evaluate serum markers for imatinib response which will be used to monitor patients during imatinib therapy. Finally, the studies will identify cell signaling pathways which remain activated in stable GIST lesions during imatinib therapy. Together, these studies will provide a better understanding as to why GIST cells persist during imatinib therapy and the insights needed to develop complementary therapies that synergize with imatinib in treating stable GIST lesions.

Priority Project E – Christopher Corless and Michael Heinrich, Oregon Health Sciences University

Secondary Imatinib Resistance

Once again, Dr. Corless and Dr. Heinrich team up to co-coordinate Project E. This project addresses the major problem of secondary resistance mechanisms in patients who have had an exemplary response to imatinib but in whom one or more GIST lesions then progress. The goals in these studies are to use various cell culture assays to understand why certain mutations are resistant to imatinib, and to identify alternate kinase inhibitors that can effectively attack these mutations. Transgenic mouse models will also be employed in these studies, to provide more comprehensive evaluations of drugs which might synergize with imatinib and assist patients who have developed imatinib resistance.

Priority Project F – Jonathan Fletcher, Harvard Medical School

Secondary Imatinib Resistance

Jonathan Fletcher has studied GIST oncogenic mechanisms for 15 years and his

group is working on novel therapeutic approaches that regulate KIT synthesis and degradation. This project will evaluate therapeutic approaches that destroy KIT oncoproteins, and will be focused initially on HSP90 inhibitors. HSP90 is required to stabilize KIT oncoproteins in GIST cells irrespective of whether the KIT oncoproteins are resistant or sensitive to imatinib. These studies will be performed in GIST cells, mouse GIST models, and in non-GIST cells transformed by genetic transfer of the types of imatinib-resistant KIT oncoproteins found in progressing GISTs.

Priority Project G – Brian Rubin, University of Washington
Murine Models

Dr. Rubin is an internationally acclaimed expert in GIST pathology and he is a leader in creating laboratory mice that develop GIST tumors. The goal of this project is to evaluate novel therapies for GIST in transgenic mice that develop GISTs because of germline KIT mutations. This project complements the studies of primary and secondary imatinib resistance in human cells (Projects D and E) but with the focus here being exclusively on *in vivo* data obtained from mouse models.

Priority Project H – Jonathan Fletcher, Harvard Medical School
Resource Development

Dr. Fletcher will coordinate the development of GIST cell lines as well as non-GIST cells (Ba/F3 cells) transformed by introduction of imatinib-sensitive and imatinib-resistant KIT genes. Collectively these resources will enable the various project investigators to investigate mechanisms of GIST imatinib resistance, and to validate new therapies that synergize with imatinib in killing GIST cells.

Priority Project I – Cristina Antonescu, Memorial Sloan-Kettering Cancer Center
Pediatric GIST

Dr. Antonescu is one of the world's leading authorities in GIST pathology, and her group has played a leadership role in characterizing the various genetic aberrations responsible for GIST. Her work is particularly focused on pediatric GISTs, which are notoriously resistant to imatinib therapy. The important goals of this study - performed by gene expression array profiling - are to identify mechanisms by which KIT is activated in pediatric GISTs, and to understand why these activation mechanisms are not subject to imatinib inhibition.

Priority Project J - Tissue Banks

The above mentioned priority research proposals will be supported by a highly annotated GIST tissue bank which will be co-led by Matt van de Rijn at Stanford (adult GIST tumors), and Cristina Antonescu at MSKCC (pediatric GIST tumors).

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			Principal Investigators and Sponsoring Instituions								
Priority Projects		Group Leaders	Antonescu MSKCC	Besmer MSKCC	Debiec-Rychter Catholic University Leuven, Belgium	Fletcher Dana-Farber/ Brigham & Young	Corless OHSU/ VA Hospital	Heinrich OHSU/ VA Hospital	Rubin University of Washington	van de Rijn Stanford University	Total
A.	Oncogenic Signaling Mechanisms	Besmer		20%	10%	20%		10%	20%	20%	100%
B.	KIT/ PDGFRA wildtype	van de Rijn				20%	20%	20%		40%	100%
C.	Primary Resistance	Corless			30%	20%		30%		20%	100%
D.	Stable Lesions	Debiec-Rychter			15%	25%	30%		10%	20%	100%
E.	Secondary Resistance	Heinrich		7.5%	25%	20%		25%	7.5%	15%	100%
F.	KIT Degradation	Fletcher		20%	20%	30%		10%	20%		100%
G.	Murine Models	Rubin		50%					50%		100%
H.	Resource Development	Fletcher		10%	20%	40%		20%	10%		100%
I.	Pediatric GIST*	Antonescu	100%								100%
J.	Tissue Banks	van de Rijn Antonescu	100% Ped							100% Adult	