



# The Research Model

*Our goal is to identify the mechanisms of GIST treatment resistance and to find the means to overcome them.*

## Background

At a historic breakfast meeting in Boston with Novartis CEO Dan Vasella and Novartis Oncology President David Epstein, Life Raft Group Executive Director Norman Scherzer proposed that Novartis help fund a major research initiative aimed at identifying and overcoming GIST resistance to therapy. In response, Vasella offered to provide the Life Raft Group with \$2 million dollars in start-up money to support this research. Since then the project has moved forward with remarkable speed.

We have assembled a world class research team that has agreed in turn to create a unique research culture. Excellence is replacing consensus and collaboration is replacing professional competition as philosophical guideposts.

To leverage our limited resources, our research team has created a strategic research plan that will enable us to direct grant funds to those research priorities with the greatest prospects of giving us the answers we need and to do so with the greatest possible speed. We believe that we have created a new research paradigm that will serve as a role model for other patient groups.

## Priority Projects

Ten priority projects have been identified. Each has been assigned a group leader who is responsible for overall coordination, reporting, and working with other group leaders to share information and appropriate data. To help bridge the gap between researcher and patient we have asked each group leader to write one brief article per year for the Life Raft Group newsletter on their area of expertise. The ten priority projects are:

**Oncogenic signaling mechanisms as novel therapeutic targets:** Identify critical parts of the KIT and PDGFRA signaling pathways that will provide synergistic and/or alternate therapeutic targets in GIST.

**KIT/PDGFR A Wildtype GISTs:** Identify the important pathways in GISTs that do not have KIT or PDGFRA mutations using methods, such as cDNA arrays and proteomics, that examine many genes at once.

**Primary Resistance:** Identify resistance mechanisms and evaluate effective therapies for GISTs that are resistant to initial Gleevec therapy. These include specific types of KIT or PDGFRA mutations called “activation loop mutants” and GISTs without mutations in KIT or PDGFRA.

**Stable disease after imatinib:** Identify the mechanisms that cause some tumors to remain stable for long periods, but prevent these tumor cells from undergoing cell death, including development of therapeutic strategies for cells that are not actively dividing (quiescent GIST cells).

**Secondary resistance mechanisms & clinical evaluation:** Evaluate new therapies for GISTs that have developed resistance to Gleevec. These crucial studies will be performed using a variety of methods, such as GIST cell cultures and other cells that have been altered to have KIT or PDGFRA mutations.

**Kit Degradation:** To examine the role of “chaperone” proteins (such as HSP90) that normally protect KIT from being destroyed within the cell, and to evaluate GIST therapies in which these proteins are inhibited, resulting in destruction of KIT.

**Mouse Imatinib Sensitive and Resistance Models:** Using mice that have been engineered with KIT mutations, evaluate therapeutic strategies to maximize initial response to Gleevec, as well as the development of resistant mice for the study of therapies for secondary resistance.

**Resource Development (imatinib sensitive & resistant):** Develop additional GIST research resources (tools) including natural GIST cell lines (Gleevec sensitive and resistant) as well as “engineered” cell lines that have been created in the lab with a variety of KIT or PDGFRA mutations.

**Pediatric GIST:** Identify the molecular mechanisms and potential drug targets for Pediatric GIST.

**Tissue Banks - We are funding two GIST tissue banks:** An adult tissue bank is being housed at Stanford University under the supervision of Matt van de Rijn and a Pediatric tissue bank is being housed at Memorial Sloan Kettering under the direction of Cristina Antonescu. Each is responsible for being the point person for the rapid transfer of tissue and data across multiple institutions. New and existing tissue from pediatric GISTs and untreated, stable and progressing adult GISTs will be collected at each tissue bank for analysis and annotation by the various research institutions. Each institution receiving grant funds will be expected to allocate up to 10% of their total grant awards to support this annotation

## Grants Infrastructure

To complement this strategic process the LRG has created a supportive grants infrastructure that holds each researcher accountable for specific results, redirects resources when research dead ends and supplements resources when new needs arise.

**Two Phases:** We have decided to proceed with a two phase grants process.

Phase one allocates the two million dollars in start-up funding by directing grant funds to those researchers best suited to implement our strategic plan. This directed research phase permits us to rapidly address those priority areas that have been determined to give us the best options for accomplishing our objectives.

Phase two will depend upon raising additional funds and may include the more traditional process of investigator driven grants.

**Indirect Costs:** Indirect costs are capped at 10% for all grants greater than \$50,000 and are completely eliminated for all grants up to \$50,000.

**Two-year grants** are being awarded but funding is committed for six months, with non-competitive renewals conditioned upon receipt of satisfactory progress reports.

**Accelerated funding:** In the event that a project completes its yearly project milestone early, the grantee will be permitted to apply for an early start for the next phase. For example, if an applicant achieves its first year project objectives at the end of nine months we would consider awarding the second year of funding three months earlier-conditioned upon the availability of funds.

**Supplemental funding:** In situations where unexpected costs hinder the successful completion of a priority project we will consider supplemental funding, contingent upon the availability of funds.

## Information Sharing

**Telecommunications:** We are primarily relying upon meeting by telecommunication to facilitate the work of the LRG Research Team.

**Listserv:** The Life Raft Group is operating a closed listserv chat facility restricted to the members of the LRG Research Team. Participants are expected to respect the confidentiality of all listserv posts. The archives of the listserv will provide a history of discussions.

**Meetings:** Every attempt will be made to hold LRG Research Team meetings in conjunction with other scheduled meetings, such as CTOS and ASCO (the two meetings most likely to draw the regular attendance of the LRG Research Team). This will further

reduce travel and administrative costs.

## **Future Plans**

**Clinical Advisory Group:** To facilitate the flow of information between the pre-clinical trial researchers of the LRG Research Team and the clinical community we are creating a Clinical Advisory Group. This will lay the foundation for a smooth interaction between laboratory based research and clinical trials.

**Research Roundtables:** We will investigate adapting research roundtables-closed door, invite only interactive sessions whereby everyone in attendance presents their unpublished work. Meeting abstract books would be disseminated to participants and a meeting summary may be submitted to peer-review journals.

**Data Bank:** In addition we will investigate the establishment of a research data bank.