

## SPOTLIGHT ON SIGNAL TRANSDUCTION INHIBITORS

### Molecular targets for therapy, signal transduction inhibition and imatinib

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We are very pleased to announce a new and exciting section in *Leukemia*, namely 'Molecular Targets for Therapy: Basic Aspects and Implications for Therapy'. I shall manage this section with a multidisciplinary team of *Leukemia* Section Editors: Drs JA McCubrey (Signal Transduction and Cytokines), D Johnson (Apoptosis), J Licht (Transcription Control and Deregulation) and JP Marie (Sensitivity and Resistance to Therapy).

We inaugurate 'Molecular Targets for Therapy' with the launch of a new Spotlight on 'Imatinib: a Model for Signal Transduction Inhibitors', Guest Editor Dr Andreas Hochhaus (see Introduction below). Like each of you in the field, we are thrilled with the results obtained so far with Imatinib (otherwise known as Glivec/Gleevec and STI571). Despite this new optimism for a rational treatment of cancer addressing specific cell regulation mechanisms, we must not forget that cancer is a shrewd enemy. When we believe that we have finally located its Achilles heel, it develops strategies for escape. Cancer is a terrorist and it must be tracked down as such. *Leukemia*, therefore, is ready for the battle ahead. Join us!

We call for manuscripts dealing with specific inhibition of signal transduction and apoptotic cascades operating in leukemic cells. As examples the manuscripts can span the scientific gamut, from basic studies performed on cell lines in cul-

ture to pre-clinical studies and clinical trials. As the mechanisms and culprits in leukemogenesis are broad, so will studies on the target genes and their products be considered. As examples, targets can be tyrosine and serine/threonine kinases, serine/threonine phosphatases, Ras/Rac GTP/GDP exchange proteins, chimeric and normal transcription factors, cytokines, angiogenic factors, apoptotic and pro-apoptotic proteins.

We have great expectations of this new section as well as the new avenues for research and particularly for treatment it will hopefully lead to. Together, we look forward to a brave new world in which sound science provides the arsenal to fight cancer.

N Muller-Bérat Killmann  
JA McCubrey

#### How to submit manuscripts

All manuscripts must be submitted, as usual, to the *Leukemia* office in Paris and labelled 'Signal Transduction Inhibition', 'Imatinib Spotlight' or 'Molecular Targets for Therapy'. They will then be assigned to the relevant editors. Authors are strongly encouraged to submit a title page and an abstract to Dr Muller-Bérat Killmann in advance of submission of the full paper to determine if their articles are appropriate for inclusion in this series and also to begin contact with potential referees. All will be done to accelerate the peer review process.

### Spotlight Imatinib: a model for signal transduction inhibitors

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The application of signal transduction inhibitors to the treatment of human malignancies has opened exciting new doors into targeted tumor therapy. Perhaps the most dramatic example of how comprehending cellular signalling pathways can lead to the development of an effective, non-toxic therapy is through the Bcr-Abl kinase inhibitor imatinib (formerly STI-571, Glivec/Gleevec). Pre-clinical studies in chronic myelogenous leukemia (CML) have demonstrated the selective inhibitory effects of imatinib against Bcr-Abl, with minimal impact on normal hematopoiesis. These promising results correlate well with the efficient inhibition also observed in both Bcr-Abl transgenic and transplanted mice.

Though imatinib is a relatively novel therapy, its successful development has been (and continues to be) painstakingly thorough. Imatinib entered clinical phase I trials in 1998 and results were published in 2001.<sup>1,2</sup> Multinational phase II studies in CML and Ph+ acute lymphoblastic leukemias (ALL) were soon initiated in 1999.<sup>3–6</sup> Imatinib is currently being compared against the traditional interferon-alpha (IFN)-plus Ara-C in a randomized trial for newly diagnosed CML patients. Preliminary phase III data were reported at the Annual Meeting of the American Society for Clinical Oncology (ASCO) in

May 2002.<sup>7</sup> Now, more than 20 000 patients have taken imatinib with encouraging clinical benefits, including high levels of tolerance to treatment.

Despite dramatic hematologic and cytogenetic responses, initial or acquired resistance to imatinib monotherapy has already become a clinical reality. Possible mechanisms of resistance to the drug were initially investigated in vitro and similar patterns were observed, at least in part, in patients.<sup>8–12</sup>

A manuscript by Dorsey *et al* will appear later in this 'Spotlight' series. They present data that identify IL-3 as a primary antagonist of Bcr-Abl inhibitor function; IL-3 protects against apoptosis induced by these compounds and as a result, may be responsible for resistance to these types of inhibitors. In order to circumvent resistance and to increase the efficacy of imatinib, combination studies with low-dose Ara-C and IFN are now in progress.

The apoptotic effect of imatinib in combination with daunorubicin on mononuclear cells *in vitro* was discussed by Tabrizi *et al*<sup>13</sup> in the June 2002 issue of *Leukemia*.

With this issue of *Leukemia*, we are launching the new Spotlight, specifically dedicated to imatinib: 'Imatinib: A Model for Signal Transduction Inhibitors'. This first round of articles includes a review of novel tyrosine kinase fusion genes in chronic myeloproliferative disorders by Nick Cross and

Andreas Reiter.<sup>14</sup> A minority of patients with Bcr-Abl negative chronic myeloproliferative disorders present with reciprocal translocations, many of which have been found to lead to activation of tyrosine kinases, most commonly PDGFR-beta or FGFR1. It is therefore likely that these diseases will also be amenable to signal transduction therapy. The second review by Paul La Rosée, Michael O'Dwyer and Brian Druker reports on current preclinical studies on the combination of imatinib with other drugs.<sup>15</sup>

We are including a research article on the first experience with imatinib therapy after autologous stem cell transplantation by Thomas Fischer and co-workers<sup>16</sup> and two letters to the editor. Mette Andersen and colleagues<sup>17</sup> describe the clonal evolution of Ph-negative hematopoiesis in CML patients after imatinib therapy with trisomy 8 in two out of three patients studied. Selle *et al*<sup>18</sup> report the successful use of imatinib in a child with Ph+ acute mixed lineage leukemia.

The intense enthusiasm associated with imatinib in the press, scientific meetings, and journals is justified when one considers the ramifications of its success and of its implications for future anti-neoplastic drug formulations. However, much work lies ahead. All aspects of the short- and long-term effects, the choice of combination with other therapeutic options, disease surveillance, and particularly, mechanisms of resistance need to be closely monitored. As such, the definitive answer as to the magnitude of superiority of imatinib over conventional treatment for CML will require many years of continued observation.

We call for all types of communications pertaining to imatinib, including letters to the editor, describing case reports with novel and interesting observations. In addition, comments on published papers will also be published as letters to the editor. We expect this Spotlight to be a platform for lively debate. Manuscripts labeled 'Imatinib Spotlight' should be submitted as usual to the central *Leukemia* office in Paris (see Introduction). Manuscripts dealing with all aspects of signal transduction inhibition in leukemias and neoplastic transformation will be published under the 'Molecular Targets for Therapy Section'.

Molecular biologists are pursuing excellence in a parallel fashion while aspiring to accelerate the transfer of knowledge in this field to treatment of patients who so desperately need it. We anxiously anticipate your participation in this endeavor.

A Hochhaus, *Guest Editor, Imatinib Spotlight*

JA McCubrey, *Section Editor, Signal Transduction and Cytokines and Signal Transduction Inhibition*

N Muller-Bérat Killmann, *Advisory Editor, Section Editor of 'Molecular Targets for Therapy'*

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