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## RESEARCH COMMUNICATION

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# Study of the Interaction Surface for the c-Src – Imatinib Complex by a Molecular Dicing Technique

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### Abstract

With the beginning of the new millennium, a new and exciting era for cancer therapy has begun with the appearance of molecular targeted drugs. Imatinib is a clinically well-tolerated small molecule that exerts selective, dual inhibition of the transforming growth factor beta (TGFbeta) and platelet-derived growth factor (PDGF) pathways. Imatinib is also suggested as a chemopreventive for recurrent and metastatic malignancies. An interesting point to be clarified regarding the mechanism of imatinib is its interaction with c-Src. Fortunately, complexing of c-Src and imatinib has recently reported, which provides a basis for further study of the interactions between the two molecules. In the present study, the author used the technique named molecular dicing to study the interaction surface between the two molecules. Accordingly, the interaction surface in c-Src and imatinib could be identified.

**Key Words :** c-Src - imatinib - molecular dicing

*Asian Pacific J Cancer Prev*, **8**, 436-437

### Introduction

With the beginning of the new millennium, a new and exciting era for cancer therapy has begun with the appearance of molecular targeted drugs (Suzuki et al., 2007). Some molecular targeting drugs, such as Glivec (Imatinib, STI571), have shown profound effects when compared to currently used chemotherapy drugs (Suzuki et al., 2007). Chronic myeloid leukemia (CML) is a clonal stem cell disorder causing many new cases annually. Research on molecular-targeted therapy confirms that specific protein kinases have broad consequences for the development of future drugs to treat CML (Ault et al., 2003). The most recent discovery is a new compound, imatinib, which has become commercially available (Ault et al, 2003). Currently, the standard of care for CML is this agent (Ault et al., 2003). Imatinib is highly effective therapy, with improving prospects over time for sustained remission and potential to severely limit or eliminate disease progression and transformation (Mauro, 2006)

Imatinib is also suggested as a chemoprevention for recurrent and metastasis malignancy (Blagosklonny, 2005; Kibble, 2007). The imatinib inhibits the tyrosine kinases c-Abl, c-Kit, and the PDGF receptor (Seeliger, 2007). However, Imatinib is less effective against c-Src, which is difficult to understand because residues interacting with imatinib in crystal structures of Abl and c-Kit are conserved in c-Src (Seeliger, 2007). This item requires further in-depth molecular research for clarification. In

this work, the author performed a molecular dicing to study the interaction surface for c-Src and imatinib by a new bioinformatics tool.

### Materials and Methods

#### *Obtaining the template structure*

The database Pubmed was used for data mining of the amino acid sequence for c-Src – imatinib complex.

#### *Determination for interaction surface by molecular dicing technique*

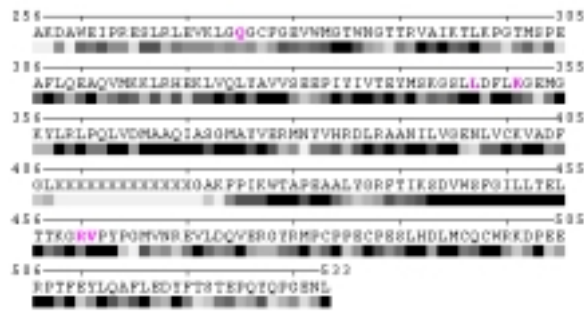
The ligand binding for Alphavbeta3 integrin was performed using a novel bioinformatic tool namely POLYVIEW (Alvarado et al., 2007). Basically, POLYVIEW can be used for identification of residues located at protein-protein interaction interfaces. Comparison of changes in relative soluble activity patterns in a protein complex relative to isolated chains is the main algorithm for determination of interaction surface.

### Results

The 3D structure for c-Src complex with imatinib (2OIQ) was derived and used as a template for further molecular dicing studies. According to the molecular dicing, the interaction surface in c-Src and imatinib could be identified (Figure 1). There are 5 interaction sites in c-Src and 6 sites in imatinib.

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## A. c-Src



## B. Imatinib



**Figure 1. Interaction Sites within the c-Src – Imatinib Complex** (\*residues in grey)

## Discussion

The development of tyrosine phosphorylation inhibitors has transformed the approach to cancer therapy and is likely to affect other fields of medicine (Porollo et al., 2004). Imatinib is a clinically well-tolerated small molecule inhibitor that exerts selective, dual inhibition of the transforming growth factor beta (TGFbeta) and platelet-derived growth factor (PDGF) pathways (Levitzi et al, 2006). Imatinib also poses activity against abl, c-kit, and is approved for the treatment of CML and gastrointestinal stromal tumors (Levitzi et al., 2006) Current progress in adoptive transfer of T cells with relative tumor specificity and disease-targeted therapy with agents especially for imatinib could prevent relapsing and make allogeneic hematopoietic cell transplantation more effective (Baron et al., 2004). Currently, there are several ongoing studies assessing the efficacy of this novel drug in the therapy of brain tumors, neuroblastoma, lung and prostate cancer (Chua et al., 2004).

An interesting point to be clarified in the mechanism of imatinib is the interaction with c-Src (Seeliger, 2007). Luckily, the complex of c-Src and imatinib has recently reported (Cowam-Jacob et al., 2005) This can help the further study on the interaction between the two molecules. The crystal structure of the c-Src kinase domain in complex with imatinib closely resembles that of Abl\*imatinib and c-Kit\*imatinib, and differs significantly from the inactive "Src/CDK" conformation of the Src family kinases (Seeliger et al, 2007). Attempts to increase the affinity of c-Src for imatinib by swapping residues with the corresponding residues in Abl have not been successful, suggesting that the thermodynamic penalty for adoption of the imatinib-binding conformation by c-Src

is distributed over a broad region of the structure (Seeliger et al, 2007). In this research, the author used the technique named molecular dicing to study the interaction surface between the two molecules. These data may be useful for further understanding of imatinib mechanisms of action against malignancies.

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