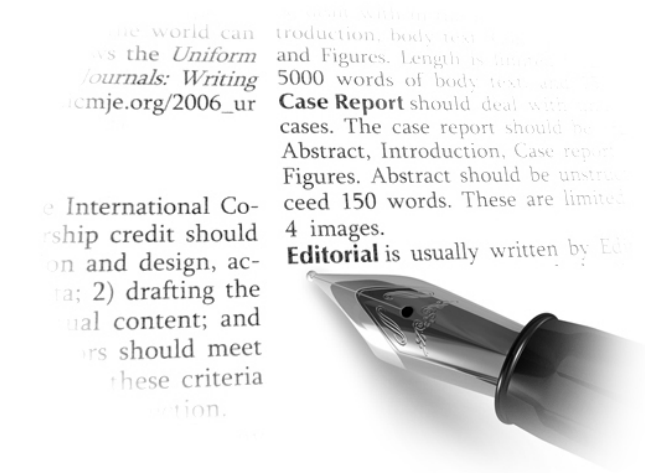

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Editorial

Targeting the protein kinases for anti-cancer therapy

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Protein kinases play a key role in regulating signal transduction and cell cycle pathways. Dysregulation of protein kinase activity is known to be an important factor in tumorigenesis, and this finding has accelerated the development of a number of novel anti-cancer agents that target this family of proteins [1]. Four groups of protein kinases are commonly described. The first group comprises the receptor tyrosine kinases including epidermal growth factor receptor, insulin-like growth factor-1 receptor, vascular endothelial growth factor receptor, fibroblast growth factor receptors 1, 3, and 4, FMS-like tyrosine kinase and c-KIT [2]. The second group comprises the non-receptor tyrosine kinases such as c-SRC, ABL1, Janus kinase 2, c-YES, and focal adhesion kinase [1-3]. The third group comprises the lipid kinases, including phosphatidylinositol 3-kinase (PI3K). A key downstream effector of PI3K is the serine-threonine kinase AKT, and the PI3K/AKT pathway is known to play an important role in cell growth and survival [4]. The fourth group comprises the serine-threonine kinases, which include proteins such as AKT, ataxia telangiectasia mutated, mammalian target of rapamycin, S6 kinase, and b-RAF and the cell cycle control kinases such as cyclin-dependent kinases, Aurora kinases, and Polo-like kinases [2].

The Aurora kinases are closely involved in the regulation of mitosis, and are overexpressed in a number of tumors. Therefore, inhibitors of these kinases are currently being investigated as a therapy for many cancers, particularly hematological malignancies [5]. There are 3 forms of human Aurora kinase: A, B, and C. Aurora kinases A and B are expressed in the majority of normal cells and are activated during the cell cycle. Aurora kinase C is now known to have complementary and overlapping functions with Aurora kinase B [6]. Ectopic overexpression of Aurora kinase A in mammalian cells induces centrosome amplification, chromosome instability, and oncogenic transformation, a phenotype that is characteristic of loss-of-function mutations of p53, and facilitates oncogenic transformation of cells by downregulating checkpoint-response pathways [7]. In the current issue of the **Korean Journal of Hematology**, Kim *et al.* reported the overexpression of Aurora kinase A in leukemic cells and that treatment of these cells with cytarabine in combination with the selective Aurora kinase A inhibitor C1368 produced a synergistic effect [8]. This is a first report of C1368 being used in a study of hematologic malignancies with specific targeting of leukemic stem cells. A combination of C1368 and cytarabine augmented apoptosis in acute myeloid leukemic cells, and the proportion of apoptosis was increased in $CD38^{+}CD34^{-}$ leukemic stem cells following stimulation with granulocyte-colony stimulating factor. This is particularly noteworthy as the chemoresistance of leukemic stem cells can often lead to primary failure after induction chemotherapy or relapse after treatment. The article by Kim *et al.* provides important information on the ability to overcome chemoresistance by combining conventional chemotherapeutic agents with protein kinase inhibitors. Other Aurora kinase inhibitors such as AZD1152, MLN8237, ENMD-2076, AS70369, KW-2449, and AT9283 have demonstrated antileukemic effects in phase I and phase II trials [5]. In particular, a

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combination of AZD1152 with cytarabine resulted in a high rate of complete remission in patients with acute myeloid leukemia who were over 60 years of age [9].

The development of novel targeting agents changed the natural history of chronic myeloid leukemia and multiple myeloma by revolutionizing the treatment of these diseases. It is tempting to dream that the development of various protein kinase inhibitors can provide a significant advancement in the treatment of acute leukemia.

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