of its evolution, hence its genetic signature. Thus genetic analyses of cancer heterogeneity would lead to distinguish those genes that drive tumor progression from those associated with relapse. More importantly, deciphering cancer genetic signatures might allow to efficiently target those tumors harbouring defined mutations that rendering them particularly sensitive to specific drugs, i.e. mutation in BRAF in melanoma, EGFR in lung cancer or mTOR in some type of breast cancer. Furthermore, analyses of cancer genetic profile not only open the way to directly targeting oncogenes themselves but also the regulatory pathway at the origin of oncogenic lesions.

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Screening of immune function inhibitors with anticancer activity from microorganisms
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Microbial and plant-derived bioactive metabolites are a treasury of organic compounds having various structures and biological activities. We have previously isolated signal transduction inhibitors such as protein-tyrosine kinase inhibitors, protein-tyrosine phosphatase inhibitors, anti-Ras compounds, and phospholipase C inhibitors from microorganisms and plants. Recently, we are more interested in inhibitors of transcription factors that are involved in the etiology of diseases. Especially, NF-kappa B appears strongly involved in many diseases including rheumatoid arthritis, arteriosclerosis, autoimmune diseases, and cancer and leukemia. Therefore, we looked for NF-kappa B inhibitors from microorganisms and plants. As a result, we designed dehydroxymethylepoxyquinomicin (DHMEQ) based on the structure of epoxyquinomicin isolated from a microorganism as an inhibitor of NF-kappa B (J. Biol. Chem. 277: 27625-27630, 2002). DHMEQ is synthesized as its racemic form, and after the chiral separation, (+)-DHMEQ is more active than (-)-DHMEQ. DHMEQ inhibited the ligand-induced or constitutively activated NF-kappa B in cultured cells. Recently, we found that DHMEQ directly binds to p65 and other Rel family proteins to inhibit the NF-kappa B functions by using SPR and MALDI-TOF-MS analyses (J. Med. Chem. 51: 5780-5788, 2008). DHMEQ showed anti-inflammatory activity in animals on rheumatoid arthritis, renal inflammation, retinal inflammation, cachexia, and allograft rejection. DHMEQ also strongly inhibited the growth of carcinoma and leukemia cells in vivo in which NF-kappa B is constitutively activated (Cancer Science 97: 990-995, 2006). For example, it effectively suppressed prostate carcinoma, thyroid carcinoma, breast carcinoma, pancreatic carcinoma, multiple myeloma, adult T-cell leukemia, AIDS-related lymphoma, and Hodgkin lymphoma in nude or SCID mice without any side effect. It is likely that the anticancer activities are due to the suppression of inflammatory reactions in tumor tissues, since its cytotoxicity is comparatively weak. In fact, DHMEQ inhibited the secretion of inflammatory cytokines from cancer cells and macrophages. DHMEQ is a very specific inhibitor of NF-kappa B, and its toxicity is low. It is now being developed as an anticancer and anti-inflammatory agent.

We have also isolated 9-methylstreptimidone from microorganisms as an NF-kappa B inhibitor (Heterocycles 69: 377-383, 2006). 9-Methylstreptimidone was shown to induce apoptosis selectively in adult T-cell leukemia cells. Very recently, we have discovered a novel AP-1 inhibitor from the derivatives of 9-methylstreptimidine. AP-1 is considered to be involved in immune functions and cancer cell growth. These cellular signal transduction inhibitors of low molecular weight may be useful as the chemical ligands to study the mechanism of diseases and also as the seeds for chemotherapeutic agents acting on the molecular targets.

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Gene Therapy in the 21st century: A progress report
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Following the advent of gene medicine in the 1980-90’s, progress has been dogged by several noticeable failures which delayed advancement of the field. More recently, progress has been observed in both somatic and cancer gene therapy. These notable moments will be highlighted. Lastly, the importance of siRNA and miRNA will be examined along with issues such as the problem of delivery of genes to patients both ex vivo and in vivo.

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Prognosis Significance of Cytokeratins-TPS, TPA compared to Tumor mass Markers in Breast Cancer
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Study aims: To evaluate the prognostic potential of Cytokeratin Tumor Markers- TPS, TPA, compared to tumor mass markers (CA15-3, CA125, CEA) and clinical status of Breast Cancer patients.

Methods and patients: The study consisted of 187 advanced Breast Cancer patients (pts), followed up for 7 years by various tumor markers and correlated to clinical parameters.

Results: A significant correlation of TPS with response to therapy, early detection (lead time) of remissions or recurrences as well as survival, were demonstrated. Univariate analysis of pretreatment marker levels (accepted cut-off levels) showed significance for TPA, TPS, CEA, CA125 and CA15-3. Median survival time of pts with low levels of CA 125, TPS, TPA, CA15-3 and CEA were 23 m, 18 m, 16.5 m, 12 m, 9.6 m as opposed to high marker levels; 8.8 m, 9 m, 8.2 m, 7.4 m, 9.7 m respectively. Survival was best correlated to low CA 125 and TPS entering levels. CA125 and TPS retained significance also in multivariate Cox’s regression analysis.

Conclusions: We conclude that the cytokeratin marker TPS (as CA 125), provide the most important information for prognosis in advanced breast cancer pts.

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Pharmacology of A Mimetic of Oxidized Glutathione
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NOV-002, a GSSG mimetic presents a novel pharmacological approach to manipulate the GSSG/GSH redox couple for therapeuti