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1. Publications

"Oxidative stress-induced biomarkers for stem cell-based chemical screening."

Yang, S. R., I. Rahman, J. E. Trosko and K. S. Kang (2012).
Prev Med 54 Suppl: S42-49.

Stem cells have been considered for their potential in pharmaceutical research, as well as for stem cell-based therapy for many diseases. Despite the potential for their use, the challenge remains to examine the safety and efficacy of stem cells for their use in therapies. Recently, oxidative stress has been strongly implicated in the functional regulation of cell behavior of stem cells. Therefore, development of rapid and sensitive biomarkers, related to oxidative stress is of growing importance in stem cell-based therapies for treating various diseases. Since stem cells have been implicated as targets for carcinogenesis and might be the origin of "cancer stem cells", understanding of how oxidative stress-induced signaling, known to be involved in the carcinogenic process could lead to potential screening of cancer chemopreventive and chemotherapeutic agents. An evaluation of antioxidant states reducing equivalents like GSH and superoxide dismutase (SOD), as well as reactive oxygen species (ROS) and nitric oxide (NO) generation, can be effective markers in stem cell-based therapies. In addition, oxidative adducts, such as 4-hydroxynonenal, can be reliable markers to detect cellular changes during self-renewal and differentiation of stem cells. This review highlights the biomarker development to monitor oxidative stress response for stem cell-based chemical screening.

"AIMP1 deficiency enhances airway hyperreactivity in mice via increased TH2 immune responses."

Hong, H. J., E. Kim, M. Y. Jung, S. Kim and T. S. Kim (2012).
Clin Immunol 143(3): 256-265.

Aminoacyl tRNA synthetase complex-interacting multicomplex protein 1 (AIMP1) is known as a novel cytokine carrying out a variety of biological activities, including angiogenesis and wound repair. In our previous reports AIMP1 was demonstrated to induce TH1 polarization. However, the effects of AIMP1 deficiency in TH1 or TH2 immune disorders remain unclear. In this study, we characterized phenotypes of AIMP1-deficient mice and investigated the role of AIMP1 in TH2-biased airway hyperreactivity. Clinical signs of allergic airway inflammation were assessed in AIMP1-deficient mice and the effects of AIMP1 deficiency on production of TH2 cytokines were evaluated in T cells using AIMP1-specific siRNA. Additionally, the enhanced pause values and histologic analysis were assessed in mice receiving AIMP1-deficient CD4+ T cells with OVA challenge. Clinical signs of spontaneous airway inflammation were noted in AIMP1-deficienct mice. AIMP1-deficient mice showed strongly increased Penh values in response to methacholine without any allergen exposure. Adoptive transfer of AIMP1-deficient CD4+ T cells to OVA-sensitized C57BL/6 mice exacerbated OVA-induced airway inflammation and investigated the role of AIMP1 in TH2-biased airway hyperreactivity. Clinical signs of allergic airway inflammation were assessed in AIMP1-deficient mice and the effects of AIMP1 deficiency on production of TH2 cytokines were evaluated in T cells using AIMP1-specific siRNA. Additionally, the enhanced pause values and histologic analysis were assessed in mice receiving AIMP1-deficient CD4+ T cells with OVA challenge. Clinical signs of spontaneous airway inflammation were noted in AIMP1-deficienct mice. AIMP1-deficient mice showed and increased infiltration of inflammatory cells into the lung. Furthermore, lung DCs in AIMP1-deficient mice showed increased expression of surface molecules, and IL-12p40 level in sera significantly decreased in AIMP1-deficient mice compared to that of wild type mice. These results strongly indicate that AIMP1 plays a role in negatively regulating TH2 responses in vivo, and AIMP1 can be employed as a novel therapeutic agent against TH2-biased diseases, particularly asthma.

"Discovery and target identification of an antiproliferative agent in live cells using fluorescence difference in two-dimensional gel electrophoresis."

Park, J., S. Oh and S. B. Park (2012).
Angew Chem Int Ed Engl 51(22): 5447-5451.

Phenotype-based screening has been recognized as a key approach to the discovery of novel therapeutic agents because of the recent withdrawal of marketed drugs developed by conventional target-based medicinal chemistry. Furthermore, the identification of small molecules that control nonconventional drug targets has become increasingly important for curing diseases that are resistant to existing drugs, for the development of regenerative medicines, and for the treatment of incurable diseases. Phenotype-based assays facilitate the use of efficiency-based evaluations for the discovery of a small-molecule modulator for unknown drug targets, which leads to the development of novel classes of drugs or the discovery of new drugable protein targets. For this approach, it is essential to identify the mode of action of small-molecule modulators. However, understanding their mechanism, the target identification process in particular, is time-consuming, difficult to implement, and does not provide clear results. Therefore, there is a great demand for the development of new and robust methods for target identification.

"Dissection of the dimerization modes in the DJ-1 superfamily."

Jung, H. J., S. Kim, Y. J. Kim, M. K. Kim, S. G. Kang, J. H. Lee, W. Kim and S. S. Cha (2012).
Mol Cells 33(2): 163-171.

The DJ-1 superfamily (DJ-1/ThiJ/PfpI superfamily) is distributed across all three kingdoms of life. These proteins are involved in a highly diverse range of cellular functions, including chaperone and protease activity. DJ-1 proteins usually form dimers or hexamers in vivo and show at least four different binding orientations via distinct interface patches. Abnormal oligomerization of human DJ-1 is related to neurodegenerative disorders including Parkinson's disease, suggesting important functional roles of quaternary structures. However, the quaternary structures of the DJ-1 superfamily have not been extensively studied. Here, we focus on the diverse oligomerization modes among the DJ-1 superfamily proteins and investigate the functional roles of quaternary structures both computationally and experimentally. The oligomerization modes are classified into 4 types (DJ-1, YhbO, Hsp, and YDR types) depending on the distinct interface patches (I-IV) upon dimerization. A unique, rotated interface via patch I is reported, which may potentially be related to higher order oligomerization. In general, the groups based on sequence similarity are consistent with the quaternary structural classes, but their biochemical functions cannot be directly inferred using sequence information alone. The observed phyletic pattern suggests the dynamic nature of quaternary structures in the course of evolution. The amino acid residues at the interfaces tend to show lower mutation rates than those of non-interfacial surfaces.

"CD49f enhances multipotency and maintains stemness through the direct regulation of OCT4 and SOX2."

Yu, K. R., S. R. Yang, J. W. Jung, H. Kim, K. Ko, D. W. Han, S. B. Park, S. W. Choi, S. K. Kang, H.

Scholer and K. S. Kang (2012). Stem Cells 30(5): 876-887.

CD49f (integrin subunit alpha6) regulates signaling pathways in a variety of cellular activities. However, the role of CD49f in regulating the differentiation and pluripotency of stem cells has not been fully investigated. Therefore, in this study, human mesenchymal stem cells (hMSCs) were induced to form spheres under nonadherent culture conditions, and we found that the CD49f-positive population was enriched in MSC spheres compared with MSCs in a monolayer. The expression of CD49f regulated the ability of hMSCs to form spheres and was associated with an activation of the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway. Furthermore, the forced expression of CD49f modulated the proliferation and differentiation potentials of hMSCs through prolonged activation of PI3K/AKT and suppressed the level of p53. We showed that the pluripotency factors OCT4 and SOX2 were recruited to the putative promoter region of CD49f, indicating that OCT4 and SOX2 play positive roles in the expression of CD49f. Indeed, CD49f expression was upregulated in human embryonic stem cells (hESCs) compared with hMSCs. The elevated level of CD49f expression was significantly decreased upon embryoid body formation in hESCs. In hESCs, the knockdown of CD49f downregulated PI3K/AKT signaling and upregulated the level of p53, inducing differentiation into three germ layers. Taken together, our data suggest that the cell-surface protein CD49f has novel and dynamic roles in regulating the differentiation potential of hMSCs and maintaining pluripotency.

"Trp-tRNA synthetase bridges DNA-PKcs to PARP-1 to link IFN-γ and p53 signaling."

Sajish, M., Q. Zhou, S. Kishi, D. M. Valdez, Jr., M. Kapoor, M. Guo, S. Lee, S. Kim, X. L. Yang and P. Schimmel (2012). Nat Chem Biol 8(6): 547-554.

Interferon-gamma (IFN-gamma) engenders strong antiproliferative responses, in part through activation of p53. However, the long-known IFN-gamma-dependent upregulation of human Trp-tRNA synthetase (TrpRS), a cytoplasmic enzyme that activates tryptophan to form Trp-AMP in the first step of protein synthesis, is unexplained. Here we report a nuclear complex of TrpRS with the catalytic subunit of DNA-dependent protein kinase (DNA-PKcs) and with poly(ADP-ribose) polymerase 1 (PARP-1), the major PARP in human cells. The IFN-gamma-dependent poly(ADP-ribosyl)ation of DNA-PKcs (which activates its kinase function) and concomitant activation of the tumor suppressor p53 were specifically prevented by Trp-SA, an analog of Trp-AMP that disrupted the TrpRS-DNA-PKcs-PARP-1 complex. The connection of TrpRS to p53 signaling in vivo was confirmed in a vertebrate system. These and further results suggest an unexpected evolutionary expansion of the protein synthesis apparatus to a nuclear role that links major signaling pathways.

"Notch1 counteracts WNT/β-catenin signaling through chromatin modification in colorectal cancer."

Kim, H. A., B. K. Koo, J. H. Cho, Y. Y. Kim, J. Seong, H. J. Chang, Y. M. Oh, D. E. Stange, J. G. Park, D. Hwang and Y. Y. Kong (2012). J Clin Invest 122(9): 3248-3259.

Crosstalk between the Notch and wingless-type MMTV integration site (WNT) signaling pathways has been investigated for many developmental processes. However, this negative correlation between Notch and WNT/beta-catenin signaling activity has been studied primarily in normal developmental and physiological processes in which negative feedback loops for both signaling pathways are intact. We found that Notch1

signaling retained the capability of suppressing the expression of WNT target genes in colorectal cancers even when beta-catenin destruction by the adenomatous polyposis coli (APC) complex was disabled. Activation of Notch1 converted high-grade adenoma into low-grade adenoma in an Apcmin mouse colon cancer model and suppressed the expression of WNT target genes in human colorectal cancer cells through epigenetic modification recruiting histone methyltransferase SET domain bifurcated 1 (SETDB1). Extensive microarray analysis of human colorectal cancers also showed a negative correlation between the Notch1 target gene, Notch-regulated ankyrin repeat protein 1 (NRARP), and WNT target genes. Notch is known to be a strong promoter of tumor initiation, but here we uncovered an unexpected suppressive role of Notch1 on WNT/beta-catenin target genes involved in colorectal cancer.

"Heteroaromatic moieties in the sphingosine backbone of alpha-Galactosylceramides for noncovalent interactions with CD1d"

Kim, Y., J. Kim, K. Oh, D. S. Lee and S. B. Park (2012). Acs Medicinal Chemistry Letters 3(2): 151-154.

A series of alpha-GalCer analogues containing heterocyclic and aromatic moieties in the sphingosine backbone were synthesized to improve the selectivity in the Th1/Th2 cytokine profile via noncovalent interaction with three aromatic residues at the binding pocket of CD1d. In vitro and in vivo biological evaluations revealed the treatment of alpha-GalCer analogue (6) induced the selective stimulation of natural killer T cells to facilitate the secretion of Th2 cytokines.

"Crystal structure of the NurA-dAMP-Mn2+ complex."

Chae, J., Y. C. Kim and Y. Cho (2012). Nucleic Acids Res 40(5): 2258-2270.

Generation of the 3' overhang is a critical event during homologous recombination (HR) repair of DNA double strand breaks. A 5'-3' nuclease, NurA, plays an important role in generating 3' single-stranded DNA during archaeal HR, together with Mre11-Rad50 and HerA. We have determined the crystal structures of apo- and dAMP-Mn(2)(+)-bound NurA from Pyrococcus furiousus (Pf NurA) to provide the basis for its cleavage mechanism. Pf NurA forms a pyramid-shaped dimer containing a large central channel on one side, which becomes narrower towards the peak of the pyramid. The structure contains a PIWI domain with high similarity to argonaute, endoV nuclease and RNase H. The two active sites, each of which contains Mn(2)(+) ion(s) and dAMP, are at the corners of the elliptical channel near the flat face of the dimer. The 3' OH group of the ribose ring is directed toward the channel entrance, explaining the 5'-3' nuclease activity of Pf NurA. We provide a DNA binding and cleavage model for Pf NurA.

"Lithographic compartmentalization of emulsion droplet templates for microparticles with multiple nanostructured compartments."

Kim, J., L. He, Y. Song, Y. Yin and S. Kwon (2012). Chem Commun (Camb) 48(49): 6091-6093.

Complicated functional microparticles with complex nanostructured compartments have been synthesized from emulsion templates by lithographic compartment allocations. Our 'top-down-bottom-up' hybrid method will provide additional material engineering capability for the synthesis of advanced functional microparticles.

"In vitro formation and characterization of a perfusable three-dimensional tubular capillary network in microfluidic devices."

Yeon, J. H., H. R. Ryu, M. Chung, Q. P. Hu and N. L. Jeon (2012). Lab Chip 12(16): 2815-2822.

This paper describes the in vitro formation and characterization of perfusable capillary networks made of human umbilical vein endothelial cells (HUVECs) in microfluidic devices (MFDs). Using this platform, an array of three-dimensional (3D) tubular capillaries of various dimensions (50-150 mum in diameter and 100-1600 mum in length) can be formed reproducibly. To generate connected blood vessels, MFDs were completely filled with fibrin gel and subsequently processed to selectively leave behind gel structures inside the bridge channels. Following gel solidification, HUVECs were coated along the gel walls, on opposite ends of the patterned 3D fibrin gel. After 3-4 days, HUVECs migrating into the fibrin gel from opposite ends fused with each other, spontaneously forming a connected vessel that expressed tight junction proteins (e.g., ZO-1), which are characteristic of post-capillary venules. With ready access to a perfusable capillary network, we demonstrated perfusion of the vessels and imaged red blood cells (RBCs) and beads flowing through them. The results were reproducible (approximately 50% successful perfusable capillaries), consistent, and could be performed in a parallel manner (9 devices per well plate). Additionally, compatibility with high resolution live-cell microscopy and the possibility of incorporating other cell types makes this a unique experimental platform for investigating basic and applied aspects of angiogenesis, anastomosis, and vascular biology.

"Osmotic stress regulates mammalian target of rapamycin (mTOR) complex 1 via c-Jun N-terminal Kinase (JNK)-mediated Raptor protein phosphorylation."

Kwak, D., S. Choi, H. Jeong, J. H. Jang, Y. Lee, H. Jeon, M. N. Lee, J. Noh, K. Cho, J. S. Yoo, D. Hwang, P. G. Suh and S. H. Ryu (2012). J Biol Chem 287(22): 18398-18407.

mTOR complex 1(mTORC1) is a multiprotein complex that integrates diverse signals including growth factors, nutrients, and stress to control cell growth. Raptor is an essential component of mTORC1 that functions to recruit specific substrates. Recently, Raptor was suggested to be a key target of regulation of mTORC1. Here, we show that Raptor is phosphorylated by JNK upon osmotic stress. We identified that osmotic stress induces the phosphorylation of Raptor at Ser-696, Thr-706, and Ser-863 using liquid chromatography-tandem mass spectrometry. We found that JNK is responsible for the phosphorylation. The inhibition of JNK abolishes the phosphorylation of Raptor induced by osmotic stress in cells. Furthermore, JNK physically associates with Raptor and phosphorylates Raptorin vitro, implying that JNK is responsible for the phosphorylation of Raptor. Finally, we found that osmotic stress activates mTORC1 kinase activity in a JNK-dependent manner. Our findings suggest that the molecular link between JNK and Raptor is a potential mechanism by which stress regulates the mTORC1 signaling pathway.

"HCF-1 self-association via an interdigitated Fn3 structure facilitates transcriptional regulatory complex formation."

Park, J., F. Lammers, W. Herr and J. J. Song (2012). Proc Natl Acad Sci U S A 109(43): 17430-17435.

Host-cell factor 1 (HCF-1) is an unusual transcriptional regulator that undergoes a process of proteolytic maturation to generate N- (HCF-1(N)) and C- (HCF-1(C)) terminal subunits noncovalently associated via self-association sequence elements. Here, we present the crystal structure of the self-association sequence 1 (SAS1) including the adjacent C-terminal HCF-1 nuclear localization signal (NLS). SAS1 elements from each of the HCF-1(N) and HCF-1(C) subunits form an interdigitated fibronectin type 3 (Fn3) tandem repeat structure. We show that the C-terminal NLS recruited by the interdigitated SAS1 structure is required for effective formation of a transcriptional regulatory complex: the herpes simplex virus VP16-induced complex. Thus, HCF-1(N)-HCF-1(C) association via an integrated Fn3 structure permits an NLS to facilitate formation of a transcriptional regulatory complex.

"CRIF1 is essential for the synthesis and insertion of oxidative phosphorylation polypeptides in the mammalian mitochondrial membrane."

Kim, S. J., M. C. Kwon, M. J. Ryu, H. K. Chung, S. Tadi, Y. K. Kim, J. M. Kim, S. H. Lee, J. H. Park, G. R. Kweon, S. W. Ryu, Y. S. Jo, C. H. Lee, H. Hatakeyama, Y. Goto, Y. H. Yim, J. Chung, Y. Y. Kong and M. Shong (2012). Cell Metab 16(2): 274-283.

Although substantial progress has been made in understanding the mechanisms underlying the expression of mtDNA-encoded polypeptides, the regulatory factors involved in mitoribosome-mediated synthesis and simultaneous insertion of mitochondrial oxidative phosphorylation (OXPHOS) polypeptides into the inner membrane of mitochondria are still unclear. In the present study, disruption of the mouse Crif1 gene, which encodes a mitochondrial protein, resulted in a profound deficiency in OXPHOS caused by the disappearance of OXPHOS subunits and complexes in vivo. CRIF1 was associated with large mitoribosomal subunits that were located close to the polypeptide exit tunnel, and the elimination of CRIF1 led to both aberrant synthesis and defective insertion of mtDNA-encoded nascent OXPHOS polypeptides into the inner membrane. CRIF1 interacted with nascent OXPHOS polypeptides and molecular chaperones, e.g., Tid1. Taken together, these results suggest that CRIF1 plays a critical role in the integration of OXPHOS polypeptides into the mitochondrial membrane in mammals.

"Variable lymphocyte receptor recognition of the immunodominant glycoprotein of Bacillus anthracis spores."

Kirchdoerfer, R. N., B. R. Herrin, B. W. Han, C. L. Turnbough, Jr., M. D. Cooper and I. A. Wilson (2012). Structure 20(3): 479-486.

Variable lymphocyte receptors (VLRs) are the adaptive immune receptors of jawless fish, which evolved adaptive immunity independent of other vertebrates. In lieu of the immunoglobulin fold-based T and B cell receptors, lymphocyte-like cells of jawless fish express VLRs(VLRA, VLRB, or VLRC) composed of leucine-rich repeats and are similar to toll-like receptors (TLRs) in structure, but antibodies (VLRB) and T cell receptors (VLRA and VLRC) in function. Here, we present the structural and biochemical characterization of VLR4, a VLRB, in complex with BclA, the immunodominant glycoprotein of Bacillus anthracis spores. Using a combination of crystallography, mutagenesis, and binding studies, we delineate the mode of antigen recognition and binding between VLR4 and BclA, examine commonalities in VLRB recognition of antigens, and demonstrate the potential of VLR4 as a diagnostic tool for the identification of B. anthracis spores.

"A prognostic model for lymph node-negative breast cancer patients based on the integration of proliferation and immunity."

Oh, E., Y. L. Choi, T. Park, S. Lee, S. J. Nam and Y. K. Shin (2012). Breast Cancer Res Treat 132(2): 499-509.

A model for a more precise prognosis of the risk of relapse is needed to avoid overtreatment of lymph node-negative breast cancer patients. A large derivation data set (n = 684) was generatedby pooling three independent breast cancer expression microarray data sets. Two major prognostic factors, proliferation and immune response, were identified among genes showing significant differential expression levels between the good outcome and poor outcome groups. For each factor, four proliferation-related genes (p-genes) and four immunity-related genes (i-genes) were selected as prognostic genes, and a prognostic model for lymph node-negative breast cancer patients was developed using a parametric survival analysis based on the lognormal distribution. The p-genes showed a predominantly negative correlation (coefficient: -0.603) with survival time, while the i-genes showed a positive correlation (coefficient: 0.243), reflecting the beneficial effect of the immune response against deleterious proliferative activity. The prognostic model shows that approximately 54% of lymph node-negative breast cancer patients were predicted to be distant metastasis-free for more than 5 years with at least 85% survival probability. The prognostic model showed a robust and high prognostic performance (HR 2.85-3.45) through three external validation data sets. Based on the integration of proliferation and immunity, the new prognostic model is expected to improve clinical decision making by providing easily interpretable survival probabilities at any time point and functional causality of the predicted prognosis with respect to proliferation and immune response.

"Gefitinib resistance of cancer cells correlated with TM4SF5-mediated epithelial-mesenchymal transition."

Lee, M. S., H. P. Kim, T. Y. Kim and J. W. Lee (2012). Biochim Biophys Acta 1823(2): 514-523.

Although cancers can be initially treated with the epidermal growth factor receptor (EGFR) inhibitor, gefitinib, continued gefitinib therapy does not benefit the survival of patients due to acquired resistance through EGFR mutations, c-MET amplification, or epithelial-mesenchymal transition (EMT). It is of further interest to determine whether mesenchymal-like, but not epithelial-like, cancer cells can become resistant to gefitinib by bypassing EGFR signaling and acquiring alternative routes of proliferative and survival signaling. Here we examined whether gefitinib resistance of cancer cells can be caused by transmembrane 4 L six family member 5 (TM4SF5), which has been shown to induce EMT via cytosolic p27Kip1 stabilization. Gefitinib-resistant cells exhibited higher and/or sustained TM4SF5 expression, cytosolic p27Kip1 stabilization, and mesenchymal phenotypes, compared with gefitinib-sensitive cells. Conversion of gefitinib-sensitive to -resistant cells by introduction of the T790M EGFR mutation caused enhanced and sustained expression of TM4SF5, phosphorylation of p27Kip1 Ser10 (responsible for cytosolic location), loss of E-cadherin from cell-cell contacts, and gefitinib-resistant EGFR and survival signaling activities. Additionally, TM4SF5 overexpression lessened the sensitivity of NSCLC cells to gefitinib. Suppression of TM4SF5 or p27Kip1 in gefitinib-resistant cells via the T790M EGFR mutation or TM4SF5 expression rendered them gefitinib-sensitive, displaying more epithelial-like and less mesenchymal-like characteristics. Together, these results indicate that TM4SF5-mediated EMT may have an important function in the gefitinib resistance of cancer cells.

"Asymmetric mode of Ca^{2+}-S100A4 interaction with nonmuscle myosin IIA generates nanomolar affinity required for filament remodeling."

Elliott, P. R., A. F. Irvine, H. S. Jung, K. Tozawa, M. W. Pastok, R. Picone, S. K. Badyal, J. Basran, P. S. Rudland, R. Barraclough, L. Y. Lian, C. R. Bagshaw, M. Kriajevska and I. L. Barsukov (2012). Structure 20(4): 654-666.

Filament assembly of nonmuscle myosin IIA (NMIIA) is selectively regulated by the small Ca(2)(+)-binding protein, S100A4, which causes enhanced cell migration and metastasis in certain cancers. Our NMR structure shows that an S100A4 dimer binds to a single myosin heavy chain in an asymmetrical configuration. NMIIA in the complex forms a continuous helix that stretches across the surface of S100A4 and engages the Ca(2)(+)-dependent binding sites of each subunit in the dimer. Synergy between these sites leads to a very tight association (K(D) approximately 1 nM) that is unique in the S100 family. Single-residue mutations that remove this synergy weaken binding and ameliorate the effects of S100A4 on NMIIA filament assembly and cell spreading in A431 human epithelial carcinoma cells. We propose a model for NMIIA filament disassembly by S100A4 in which initial binding to the unstructured NMIIA tail initiates unzipping of the coiled coil and disruption of filament packing.

"Cancer association study of aminoacyl-tRNA synthetase signaling network in glioblastoma."

Kim, Y. W., C. Kwon, J. L. Liu, S. H. Kim and S. Kim (2012). PLoS One 7(8): e40960.

Aminoacyl-tRNA synthetases (ARSs) and ARS-interacting multifunctional proteins (AIMPs) exhibit remarkable functional versatility beyond their catalytic activities in protein synthesis. Their non-canonical functions have been pathologically linked to cancers. Here we described our integrative genome-wide analysis of ARSs to

show cancer-associated activities in glioblastoma multiforme (GBM), the most aggressive malignant primary brain tumor. We first selected 23 ARS/AIMPs (together referred to as ARSN), 124 cancer-associated druggable target genes (DTGs) and 404 protein-protein interactors (PPIs) of ARSsusing NCI's cancer gene index. 254 GBM affymetrix microarray data in The Cancer Genome Atlas (TCGA) were used to identify the probe sets whose expression were most strongly correlated with survival (Kaplan-Meier plots versus survival times, log-rank t-test <0.05). The analysis identified 122 probe sets as survival signatures, including 5 of ARSN (VARS, QARS, CARS, NARS, FARS), and 115 of DTGs and PPIs (PARD3, RXRB, ATP5C1, HSP90AA1, CD44, THRA, TRAF2, KRT10, MED12, etc). Of note, 61 survival-related probeswere differentially expressed in three different prognosis subgroups in GBM patients and showed correlation with established prognosis markers such as age and phenotypic molecular signatures. CARS and FARS also showed significantly higher association with different molecular networks in GBM patients. Taken together, our findings demonstrate evidence for an ARSN biology-dominant contribution in the biology of GBM.

"CDA: combinatorial drug discovery using transcriptional response modules."

Lee, J. H., D. G. Kim, T. J. Bae, K. Rho, J. T. Kim, J. J. Lee, Y. Jang, B. C. Kim, K. M. Park and S. Kim (2012). PLoS One 7(8): e42573.

BACKGROUND: Anticancer therapies that target single signal transduction pathways often fail to prevent proliferation of cancer cells because of overlapping functions and cross-talk between different signaling pathways. Recent research has identified that balanced multi-component therapies might be more efficacious than highly specific single component therapies in certain cases. Ideally, synergistic combinations can provide 1) increased efficacy of the therapeutic effect 2) reduced toxicity as a result of decreased dosage providing equivalent or increased efficacy 3) the avoidance or delayed onset of drug resistance. Therefore, the interest in combinatorial drug discovery based on systems-oriented approaches has been increasing steadily in recent years. METHODOLOGY: Here we describe the development of Combinatorial Drug Assembler (CDA), a genomics and bioinformatics system, whereby using gene expression profiling, multiple signaling pathways are targeted for combinatorial drug discovery. CDA performs expression pattern matching of signaling pathway components to compare genes expressed in an input cell line (or patient sample data), with expression patterns in cell lines treated with different small molecules. Then it detects best pattern matching combinatorial drug pairs across the input gene set-related signaling pathways to detect where gene expression patterns overlap and those predicted drug pairs could likely be applied as combination therapy. We carried out in vitro validations on non-small cell lung cancer cells and triple-negative breast cancer (TNBC) cells. We found two combinatorial drug pairs that showed synergistic effect on lung cancer cells. Furthermore, we also observed that halofantrine and vinblastine were synergistic on TNBC cells. CONCLUSIONS: CDA provides a new way for rational drug combination. Together with phExplorer, CDA also provides functional insights into combinatorial drugs. CDA is freely available at http://cda.i-pharm.org.

"Identification of CD23 as a functional receptor for the proinflammatory cytokine AIMP1/p43."

Kwon, H. S., M. C. Park, D. G. Kim, K. Cho, Y. W. Park, J. M. Han and S. Kim (2012). J Cell Sci 125(Pt 19): 4620-4629.

Aminoacyl-tRNA-synthetase-interacting multifunctional protein 1 (AIMP1/p43) can be secreted to trigger proinflammatory molecules while it is predominantly bound to a cytoplasmic macromolecular protein complex that contains several different aminoacyl-tRNA synthetases. Although its activities as a secreted signaling factor have been well characterized, the functional receptor for its proinflammatory activity has not yet identified. In this study, we have identified the receptor molecule for AIMP1 that mediates the secretion of TNF-alpha from THP-1 monocytic cells and primary human peripheral blood mononuclear cells (PBMCs). In a screen of 499 soluble receptorswe identified CD23, a known low-affinity receptor for IgE, as a high affinity binding partner of AIMP1. We found that downregulation of CD23 attenuated AIMP1-induced TNF-alpha secretion and AIMP1 binding to THP-1 and PBMCs. We also observed that in THP-1 and PBMCs, AIMP1-induced TNF-alpha secretion, mediated by CD23, involved activation of ERK1/2. Interestingly, endothelial monocyte activating polypeptide II (EMAP II), the C-terminal fragment of AIMP1 that is also known to work as a proinflammatory cytokine, was incapable of binding to CD23 and of activating ERK1/2. Therefore, identification of CD23 not only explains the inflammatory function of AIMP1 but also provides the first evidence by which the mode of action of AIMP1 can be distinguished from that of its C-terminal domain, EMAP II.

"A potent small-molecule inducer of chondrogenic differentiation of human bone marrow-derived mesenchymal stem cells"

Cho, T. J., J. Kim, S. K. Kwon, K. Oh, J. A. Lee, D. S. Lee, J. Cho and S. B. Park (2012). Chemical Science 3(10): 3071-3075.

We discovered a novel small-molecule modulator 5{i,2} that can specifically induce the chondrogenic differentiation of human bone marrow-derived mesenchymal stem cells (hBM-MSCs). Based on our biochemical and histological studies, 5{i,2} showed more of a directed differentiation of MSCs to chondrocyte balls compared to TGF-beta 3.

"Mechanism of anchoring of OmpA protein to the cell wall peptidoglycan of the gram-negative bacterial outer membrane."

Park, J. S., W. C. Lee, K. J. Yeo, K. S. Ryu, M. Kumarasiri, D. Hesek, M. Lee, S. Mobashery, J. H. Song, S. I. Kim, J. C. Lee, C. Cheong, Y. H. Jeon and H. Y. Kim (2012). FASEB J 26(1): 219-228.

The outer membrane protein A (OmpA) plays important roles in anchoring of the outer membrane to the bacterial cell wall. The C-terminal periplasmic domain of OmpA (OmpA-like domain) associates with the peptidoglycan (PGN) layer noncovalently. However, there is a paucity of information on the structural aspects of the mechanism of PGN recognition by OmpA-like domains. To elucidate this molecular recognition process, we solved the high-resolution crystal structure of an OmpA-like domain from Acinetobacter baumannii bound to diaminopimelate (DAP), a unique bacterial amino acid from the PGN. The structure clearly illustrates that two absolutely conserved Asp271 and Arg286 residues are the key to the binding to DAP of PGN. Identification of DAP as the central anchoring site of PGN to OmpA is further supported by isothermal titration calorimetry and a pulldown assay with PGN. An NMR-based computational model for

complexation between the PGN and OmpA emerged, and this model is validated by determining the crystal structure in complex with a synthetic PGN fragment. These structural data provide a detailed glimpse of how the anchoring of OmpA to the cell wall of gram-negative bacteria takes place in a DAP-dependent manner.

"Rational drug repositioning guided by an integrated pharmacological network of protein, disease and drug."

Lee, H. S., T. Bae, J. H. Lee, D. G. Kim, Y. S. Oh, Y. Jang, J. T. Kim, J. J. Lee, A. Innocenti, C. T. Supuran, L. Chen, K. Rho and S. Kim (2012). BMC Syst Biol 6: 80.

BACKGROUND: The process of drug discovery and development is time-consuming and costly, and the probability of success is low. Therefore, there is rising interest in repositioning existing drugs for new medical indications. When successful, this processreduces the risk of failure and costs associated with de novo drug development. However, in many cases, new indications of existing drugs have been found serendipitously. Thus there is a clear need for establishment of rational methods for drug repositioning. RESULTS: In this study, we have established a database we call "PharmDB" which integrates data associated with disease indications, drug development, and associated proteins, and known interactions extracted from various established databases. To explore linkages of known drugs to diseases of interest from within PharmDB, we designed the Shared Neighborhood Scoring (SNS) algorithm. And to facilitate exploration of tripartite (Drug-Protein-Disease) network, we developed a graphical data visualization software program called phExplorer, which allows us to browse PharmDB data in an interactive and dynamic manner. We validated this knowledge-based tool kit, by identifying a potential application of a hypertension drug, benzthiazide (TBZT), to induce lung cancer cell death. CONCLUSIONS: By combining PharmDB, an integrated tripartite database, with Shared Neighborhood Scoring (SNS) algorithm, we developed a knowledge platform to rationally identify new indications for known FDA approved drugs, which can be customized to specific projects using manual curation. The data in PharmDB is open access and can be easily explored with phExplorer and accessed via BioMart web service (http://www.i-pharm.org/, http://biomart.i-pharm.org/).

"Splicing variant of AIMP2 as an effective target against chemoresistant ovarian cancer."

Choi, J. W., J. W. Lee, J. K. Kim, H. K. Jeon, J. J. Choi, D. G. Kim, B. G. Kim, D. H. Nam, H. J. Kim, S. H. Yun and S. Kim (2012). J Mol Cell Biol 4(3): 164-173.

Chemoresistance is a main cause for the failure of cancer management and intensive investigation is on-going to control chemoresistant (CR) cancers. Although NF-kappaB has been suggested as one of the potential targets to alleviate chemoresistance of epithelial ovarian cancer (EOC), direct targeting of NF-kappaB may result in an unexpected effect due to the complex regulatory network via NF-kappaB. Here we show that AIMP2-DX2, a splicing variant of tumor suppressor AIMP2, can be a therapeutic target to control CR EOC. AIMP2-DX2 was often highly expressed in CR EOC both in vitro and in vivo. AIMP2-DX2 compromised the tumor necrosis factor alpha-dependent pro-apoptotic activity of AIMP2 via the competitive inhibition of AIMP2 binding to TRAF2 that plays a pivotal role in the regulation of NF-kappaB. The direct delivery of siRNA against AIMP2-DX2 into abdominal metastatic tumors of ovarian cancer using a microneedle converged on microendoscopy significantly suppressed the growth rate of tumors. The treated cancer tissues showed an enhanced apoptosis and the decreased TRAF2 level. Thus, we suggest that the downregulation of AIMP2-DX2 can be a potent adjuvant therapeutic approach for CR EOC that resulted from an aberrant activity of NF-kappaB.

"JNK signaling activity regulates cell-cell adhesions via TM4SF5-mediated p27(Kip1) phosphorylation."

Kim, H., O. Jung, M. Kang, M. S. Lee, D. Jeong, J. Ryu, Y. Ko, Y. J. Choi and J. W. Lee (2012). Cancer Lett 314(2): 198-205.

Transmembrane 4L six family member 5 (TM4SF5) can regulate cell-cell adhesion and cellular morphology via cytoplasmic p27(Kip1)-mediated changes in RhoA activity. However, how TM4SF5 causes cytosolic p27(Kip1) stabilization remains unknown. In this study we found that TM4SF5-mediated Ser10 phosphorylation of p27(Kip1) required for cytosolic localization was not always correlated with Akt activity. Inhibition or suppression of c-Jun N-terminal kinase (JNK) in TM4SF5-expressing cells decreased Ser10 phosphorylation of p27(Kip1) and rescued expression levels and localization of adherence junction molecules to cell-cell contacts. These observations suggest involvement of JNKs in TM4SF5-mediated p27(Kip1) Ser10 phosphorylation and localization during epithelial-mesenchymal transition.

"Interaction of two translational components, lysyl-tRNA synthetase and p40/37LRP, in plasma membrane promotes laminin-dependent cell migration."

Kim, D. G., J. W. Choi, J. Y. Lee, H. Kim, Y. S. Oh, J. W. Lee, Y. K. Tak, J. M. Song, E. Razin, S. H. Yun and S. Kim (2012). FASEB J 26(10): 4142-4159.

Although human lysyl-tRNA synthetase (KRS), an enzyme for protein synthesis, is often highly expressed in various cancer cells, its pathophysiological implications have not been understood. Here we found that KRS induces cancer cell migration through interaction with the 67-kDa laminin receptor (67LR) that is converted from ribosomal subunit p40. On laminin signal, KRS was phosphorylated at the T52 residue by p38MAPK and dissociated from the cytosolic multi-tRNA synthetase complex for membrane translocation. The importance of T52 phosphorylation for membrane translocation of KRS was confirmed by site-directed mutagenesis. In the membrane, turnover of 67LR was controlled by Nedd4-mediated ubiquitination, andKRS inhibited ubiquitin-dependent degradation of 67LR, thereby enhancing laminin-induced cell migration. This work thus unveiled a unique function of KRS in the control of cell migration and its pathological implication in metastasis.

"Srs2 possesses a non-canonical PIP box in front of its SBM for precise recognition of SUMOylated PCNA."

Kim, S. O., H. Yoon, S. O. Park, M. Lee, J. S. Shin, K. S. Ryu, J. O. Lee, Y. S. Seo, H. S. Jung and B. S. Choi (2012). J Mol Cell Biol 4(4): 258-261.

Completion of DNA replication needs to be ensured even when challenged with fork progression problems or DNA damage. PCNA and its modifications constitute a molecular switch to control distinct repair pathways. In yeast, SUMOylated PCNA (S-PCNA) recruits Srs2 to sites of replication where Srs2 can disrupt Rad51 filaments and prevent homologous recombination (HR). We report here an unexpected additional mechanism by which S-PCNA and Srs2 block the synthesis-dependent extension of a recombination intermediate, thus limiting its potentially hazardous resolution in association with a cross-over. This new Srs2 activity requires the SUMO interaction motif at its C-terminus, but neither its translocase activity nor its interaction with Rad51. Srs2 binding to S-PCNA dissociates Pol□ and Pol□ from the repair synthesis machinery, thus revealing a novel regulatory mechanism controlling spontaneous genome rearrangements. Our results suggest that cycling cells use the Siz1-dependent SUMOylation of PCNA to limit the extension of repair synthesis during template switch or HR and attenuate reciprocal DNA strand exchanges to maintain genome stability.

"Leucyl-tRNA synthetase is an intracellular leucine sensor for the mTORC1-signaling pathway."

Han, J. M., S. J. Jeong, M. C. Park, G. Kim, N. H. Kwon, H. K. Kim, S. H. Ha, S. H. Ryu and S. Kim (2012). Cell 149(2): 410-424.

Amino acids are required for activation of the mammalian target of rapamycin (mTOR) kinase, which regulates protein translation, cell size, and autophagy. However, the amino acid sensor that directly couples intracellular amino acid-mediated signaling to mTORC1 is unknown. Here we show that leucyl-tRNA synthetase (LRS) plays a critical role in amino acid-induced mTORC1 activation by sensing intracellular leucine concentration and initiating molecular events leading to mTORC1 activation. Mutation of LRS amino acid residues important for leucine bindingrenders the mTORC1 pathway insensitive to intracellular levels of amino acids. We show that LRS directly binds to Rag GTPase, the mediator of amino acid signaling to mTORC1, in an amino acid-dependent manner and functions as a GTPase-activating protein (GAP) for Rag GTPase to activate mTORC1. This work demonstrates that LRS is a key mediator for amino acid signaling to mTORC1.

"Secretion of ATP from Schwann cells through lysosomal exocytosis during Wallerian degeneration."

Shin, Y. H., S. J. Lee and J. Jung (2012). Biochem Biophys Res Commun 429(3-4): 163-167.

The present study demonstrates that adenosine triphosphate (ATP) is released from Schwann cells through lysosomal exocytosis during Wallerian degeneration and in response to stimulation. In primary Schwann cell cultures, ATP was stored in lysosomal vesicles. ATP could then induce Ca(2+)-dependent lysosomal exocytosis. Among three stimulants of lysosomal exocytosis (glutamate, NH(4)Cl and zymosan), only NH(4)Cl was sufficient to induce ATP release from ex vivo sciatic nerve explants at 3 days in vitro. Lysosomal exocytosis inhibitors (metformin, chlorpromazine and vacuolin-1) reversed the effect of NH(4)Cl-enhanced ATP release, replicating the state of explants treated with NH(4)Cl in the absence of lysosomal exocytosis inhibitors. Furthermore, we observed ATP release through lysosomal exocytosis during Wallerian degeneration in sciatic explant cultures using the recently identified vesicular nucleotide transporter (VNUT). From these experiments, we conclude that the exocytosis of lysosomes in Schwann cells during Wallerian degeneration is Ca(2+)-dependent, and that it induces ATP release from Schwann cells.

"Lithographically encoded polymer microtaggant using high-capacity and error-correctable QR code for anti-counterfeiting of drugs."

Han, S., H. J. Bae, J. Kim, S. Shin, S. E. Choi, S. H. Lee, S. Kwon and W. Park (2012). Adv Mater 24(44): 5924-5929.

A QR-coded microtaggant for the anti-counterfeiting of drugs is proposed that can provide high capacity and error-correction capability. It is fabricated lithographically in a microfluidic channel with special consideration of the island patterns in the QR Code. The microtaggant is incorporated in the drug capsule ("on-dose authentication") and can be read by a simple smartphone QR Code reader application when removed from the capsule and washed free of drug.

"Cross-talk between TGFβ1 and EGFR signalling pathways induces TM4SF5 expression and epithelial-mesenchymal transition."

Kang, M., S. Choi, S. J. Jeong, S. A. Lee, T. K. Kwak, H. Kim, O. Jung, M. S. Lee, Y. Ko, J. Ryu, Y. J. Choi, D. Jeong, H. J. Lee, S. K. Ye, S. H. Kim and J. W. Lee (2012). Biochem J 443(3): 691-700.

The EMT (epithelial-mesenchymal transition) is involved in fibrosis and cancer, and is regulated by different signalling pathways mediated through soluble factors, actin reorganization and transcription factor actions. Because the tetraspan (also called tetraspanin) TM4SF5 (transmembrane 4 L6 family member 5) is highly expressed in hepatocellular carcinoma and induces EMT, understanding how TM4SF5 expression in hepatocytes is regulated is important. We explored the mechanisms that induce TM4SF5 expression and whether impaired signalling pathways for TM4SF5 expression inhibit the acquisition of mesenchymal cell features, using human and mouse normal hepatocytes. We found that TGFbeta1 (transforming growth factor beta1)-mediated Smad activation caused TM4SF5 expression and EMT, and activation of the EGFR [EGF (epidermal growth factor) receptor] pathway. Inhibition of EGFR activity following TGFbeta1 treatment abolished acquisition of EMT, suggesting a link from Smads to EGFR for TM4SF5 expression. Further, TGFbeta1-mediated EGFR activation and TM4SF5 expression were abolished by EGFR suppression or extracellular EGF depletion. Smad overexpression mediated EGFR activation and TM4SF5 expression in the absence of serum, and EGFR kinase inactivation or EGF depletion abolished Smad-overexpression-induced TM4SF5 and mesenchymal cell marker expression. Inhibition of Smad, EGFR or TM4SF5 using Smad7 or small compounds also blocked TM4SF5 expression and/or EMT. These results indicate that TGFbeta1- and growth factor-mediated signalling activities mediate TM4SF5 expression leading to acquisition of mesenchymal cell features, suggesting that TM4SF5 induction may be involved in the development of liver pathologies.

"Crystal structure of tandem ACT domain-containing protein ACTP from Galdieria sulphuraria."

Bitto, E., J. Kim do, C. A. Bingman, H. J. Kim, B. W. Han and G. N. Phillips, Jr. (2012).

Proteins 80(8): 2105-2109.

The ACT domain is a structurally conserved small molecule binding domain which is mostly involved in amino acid and purine metabolism. Here, we report the crystal structure of a tandem ACT domain-containing protein (ACTP) from Galdieria sulphuraria. The two ACTP monomers in the asymmetric unit form a dimer with a non-crystallographic twofold axis in a domain-swapped manner, showing a horseshoe-like structure with a central crevice. This structure contributes to expand our knowledge on the structural diversity of ACT domain-containing proteins.

"Secreted human glycyl-tRNA synthetase implicated in defense against ERK-activated tumorigenesis."

Park, M. C., T. Kang, D. Jin, J. M. Han, S. B. Kim, Y. J. Park, K. Cho, Y. W. Park, M. Guo, W. He, X. L. Yang, P. Schimmel and S. Kim (2012). Proc Natl Acad Sci U S A 109(11): E640-647.

Although adaptive systems of immunity against tumor initiation and destruction are well investigated, less understood is the role, if any, of endogenous factors that have conventional functions. Here we show that glycyl-tRNA synthetase (GRS), an essential component of the translation apparatus, circulates in serum and can be secreted from macrophages in response to Fas ligand that is released from tumor cells. Through cadherin (CDH)6 (K-cadherin), GRS bound to different ERK-activated tumor cells, and released phosphatase 2A (PP2A) from CDH6. The activated PP2A then suppressed ERK signaling through dephosphorylation of ERK and induced apoptosis. These activities were inhibited by blocking GRS with a soluble fragment of CDH6. With in vivo administration of GRS, growth of tumorswith a high level of CDH6 and ERK activation were strongly suppressed. Our results implicate a conventional cytoplasmic enzyme in translation as an intrinsic component of the defense against ERK-activated tumor formation.

"Chemical modulators working at pharmacological interface of target proteins."

Jeon, Y. H., J. Y. Lee and S. Kim (2012). Bioorg Med Chem 20(6): 1893-1901.

For last few decades, the active site cleft and substrate-binding site of enzymes as well as ligand-binding site of the receptors have served as the main pharmacological space for drug discovery. However, rapid accumulation of proteome and protein network analysis data has opened a new therapeutic space that is the interface between the interacting proteins. Due to the complexity of the interaction modes and the numbers of the participating components, it is still challenging to identify the chemicals that can accurately control the protein-protein interactions at desire. Nonetheless, the number of chemical drugs and candidates working at the interface of the interacting proteins are rapidly increasing. This review addresses the current case studies and state-of-the-arts in the development of small chemical modulators controlling the interactions of the proteins that have pathological implications in various human diseases such as cancer, immune disorders, neurodegenerative and infectious diseases.

"Breast density change as a predictive surrogate for response to adjuvant endocrine therapy in hormone receptor positive breast cancer."

Kim, J., W. Han, H. G. Moon, S. K. Ahn, H. C. Shin, J. M. You, S. W. Han, S. A. Im, T. Y. Kim, H. R. Koo, J. M. Chang, N. Cho, W. K. Moon and D. Y. Noh (2012). Breast Cancer Res 14(4): R102.

Anti-estrogen therapy has been shown to reduce mammographic breast density (MD). We hypothesized that a short-term change in breast density may be a surrogate biomarker predicting response to adjuvant endocrine therapy (ET) in breast cancer. METHODS: We analyzed data for 1,065 estrogen receptor (ER)-positive breast cancer patients who underwent surgery between 2003 and 2006 and received at least 2 years of ET, including tamoxifen and aromatase inhibitors. MD was measured using Cumulus software 4.0 and expressed as a percentage. MD reduction (MDR) was defined as the absolute difference in MD of mammograms taken preoperatively and 8-20 months after the start of ET. RESULTS: At a median follow-up of 68.8 months, the overall breast cancer recurrence rate was 7.5% (80/1065). Mean MDR was 5.9% (range, -17.2% to 36.9%). Logistic regression analysis showed that age < 50 years, high preoperative MD, and long interval between start of ET to follow-up mammogram were significantly associated with larger MDR ($p < 0.05$). In a survival analysis, tumor size, lymph node positivity, high Ki-67 (>/= 10%), and low MDR were independent factors significantly associated with recurrence-free survival ($p < 0.05$). Compared with the group showing the greatest MDR (>/= 10%), the hazard ratios for MDRs of 5-10%, 0-5%, and < 0% were 1.33, 1.92, and 2.26, respectively. CONCLUSIONS: MD change during short-term use of adjuvant ET was a significant predictor of long-term recurrence in women with ER-positive breast cancer. Effective treatment strategies are urgently needed in patients with low MDR despite about 1 year of ET.

"Cell adhesion-dependent serine 85 phosphorylation of paxillin modulates focal adhesion formation and haptotactic migration via association with the C-terminal tail domain of talin."

Kwak, T. K., M. S. Lee, J. Ryu, Y. J. Choi, M. Kang, D. Jeong and J. W. Lee (2012). J Biol Chem 287(33): 27499-27509.

Integrin-mediated adhesion to extracellular matrix proteins is dynamically regulated during morphological changes and cell migration. Upon cell adhesion, protein-protein interactions among molecules at focal adhesions (FAs) play major roles in the regulation of cell morphogenesis and migration. Although tyrosine phosphorylation of paxillin is critically involved in adhesion-mediated signaling, the significance of paxillin phosphorylation at Ser-85 and the mechanism by which it regulates cell migration remain unclear. In this study, we examined how Ser-85 phosphorylation of paxillin affects FA formation and cell migration. We found that paxillin phosphorylation at Ser-85 occurred during HeLa cell adhesion to collagen I and was concomitant with tyrosine phosphorylation of both focal adhesion kinase and talin. However, the non-phosphorylatable S85A mutant of paxillin impaired cell spreading, FA turnover, and migration toward collagen I but not toward serum. Furthermore, whereas the (presumably indirect) interaction between paxillin and the C-terminal tail of talin led to dynamic FAs at the cell boundary, S85A paxillin did not bind talin and caused stabilized FAs in the central region of cells. Together, these observations suggest that cell adhesion-dependent Ser-85 phosphorylation of paxillin is important for its interaction with talin and regulation of dynamic FAs and cell migration.

"Validation of a scoring system for predicting malignancy in patients diagnosed with atypical ductal hyperplasia using an ultrasound-guided core needle biopsy."

Kim, J., W. Han, E. Y. Go, H. G. Moon, S. K. Ahn, H. C. Shin, J. M. You, J. M. Chang, N. Cho, W. K. Moon, I. A. Park and D. Y. Noh (2012). J Breast Cancer 15(4): 407-411.

PURPOSE: The need for surgical excision in patients with ultrasound-guided core needle biopsy (CNB)-diagnosed atypical ductal hyperplasia (ADH) remains an issue of debate. The present study sought to validate a scoring system (the U score, for underestimation) that we have previously developed for predicting malignancy in CNB-diagnosed ADH. METHODS: The study prospectively enrolled 85 female patients with CNB-diagnosed ADH who underwent subsequent surgical excision. Underestimation was defined as a surgical specimen having malignant foci. RESULTS: The overall underestimation rate was 37% (31/85). Multivariate analysis showed that a clinically palpable mass, microcalcification on imaging, size >15 mm and a patient age of >/=50 years were independently associated with underestimation. When applied to the scoring system, the validation score was significant (p<0.001; area under the curve, 0.852). No patient with a U score <3.5 had an underestimated lesion. CONCLUSION: The present study successfully validated the efficacy of our scoring system for predicting malignancy in CNB-diagnosed ADH. A U score of </=3.5 indicates that surgical excision may not be necessary.

"AIMP3/p18 controls translational initiation by mediating the delivery of charged initiator tRNA to initiation complex."

Kang, T., N. H. Kwon, J. Y. Lee, M. C. Park, E. Kang, H. H. Kim, T. J. Kang and S. Kim (2012). J Mol Biol 423(4): 475-481.

Aminoacyl-tRNA synthetase-interacting multifunctional proteins (AIMPs) are nonenzymatic scaffolding proteins that comprise multisynthetase complex (MSC) with nine aminoacyl-tRNA synthetases in higher eukaryotes. Among the three AIMPs, AIMP3/p18 is strongly anchoredto methionyl-tRNA synthetase (MRS) in the MSC. MRS attaches methionine (Met) to initiator tRNA (tRNA(i)(Met)) and plays an important role in translation initiation. It is known that AIMP3 is dispatched to nucleus or nuclear membrane to induce DNA damage response or senescence; however, the role of AIMP3 in translation as a component of MSC and the meaning of its interaction with MRS are still unclear. Herein, we observed that AIMP3 specifically interacted with Met-tRNA(i)(Met)in vitro, while it showed little or reduced interaction with unacylated or lysine-charged tRNA(i)(Met). In addition, AIMP3 discriminates Met-tRNA(i)(Met) from Met-charged elongator tRNA based on filter-binding assay. Pull-down assay revealed that AIMP3 and MRS had noncompetitive interaction with eukaryotic initiation factor 2 (eIF2) gamma subunit (eIF2gamma), which is in charge of binding with Met-tRNA(i)(Met) for the delivery of Met-tRNA(i)(Met) to ribosome. AIMP3 recruited active eIF2gamma to the MRS-AIMP3 complex, and the level of Met-tRNA(i)(Met) bound to eIF2 complex was reduced by AIMP3 knockdown resulting in reduced protein synthesis. All these results suggested the novel function of AIMP3 as a critical mediator of Met-tRNA(i)(Met) transfer from MRS to eIF2 complex for the accurate and efficient translation initiation.

"Free-floating amphiphilic picoliter droplet carriers for multiplexed liquid loading in a microfluidic channel."

Park, W., S. Han, H. Lee and S. Kwon (2012). Microfluidics and Nanofluidics 13(3): 511-518.

We present free-floating amphiphilic picoliter microcarriers for multiplexed loading in a microfluidic device. The amphiphilic microcarrier is composed of encoded hydrophobic hexagonal outer structure and hydrophilic inner structure. We fabricate these free-floating droplet carriers and assemble them in a microfluidic device for a demonstration of multiplexed liquid loading. Picoliter loading is performed by serial solution exchange of aqueous and oil phase solution. We are able to precisely adjust the loaded volume by varying the diameter and depth of the microcarrier. We also fabricate arbitrary shaped microwells and load picoliter droplets into them. A microbead suspension is also used to demonstrate mixing via continuous oil flow. Further development of this work may be applicable to high-throughput multiplexed assays using quantized liquid loading in a microfluidic environment.

"Tetraspan TM4SF5-dependent direct activation of FAK and metastatic potential of hepatocarcinoma cells."

Jung, O., S. Choi, S. B. Jang, S. A. Lee, S. T. Lim, Y. J. Choi, H. J. Kim, D. H. Kim, T. K. Kwak, H. Kim, M. Kang, M. S. Lee, S. Y. Park, J. Ryu, D. Jeong, H. K. Cheong, K. H. Park, B. J. Lee, D. D. Schlaepfer and J. W. Lee (2012). J Cell Sci 125(Pt 24): 5960-5973.

Transmembrane 4 L six family member 5 (TM4SF5) plays an important role in cell migration, and focal adhesion kinase (FAK) activity is essential for homeostatic and pathological migration of adherent cells. However, it is unclear how TM4SF5 signaling mediates the activation of cellular migration machinery, and how FAK is activated during cell adhesion. Here, we showed that direct and adhesion-dependent binding of TM4SF5 to FAK causes a structural alteration that may release the inhibitory intramolecular interaction in FAK. In turn, this may activate FAK at the cell's leading edge, to promote migration/invasion and in vivo metastasis. TM4SF5-mediated FAK activation occurred during integrin-mediated cell adhesion. TM4SF5 was localized at the leading edge of the cells, together with FAK and actin-organizing molecules, indicating a signaling link between TM4SF5/FAK and actin reorganization machinery. Impaired interactions between TM4SF5 and FAK resulted in an attenuated FAK phosphorylation (the signaling link to actin organization machinery) and the metastatic potential. Our findings demonstrate that TM4SF5 directly binds to and activates FAK in an adhesion-dependent manner, to regulate cell migration and invasion, suggesting that TM4SF5 is a promising target in the treatment of metastatic cancer.

"hiPathDB: a human-integrated pathway database with facile visualization."

Yu, N., J. Seo, K. Rho, Y. Jang, J. Park, W. K. Kim and S. Lee (2012). Nucleic Acids Res 40(Database issue): D797-802.

One of the biggest challenges in the study of biological regulatory networks is the systematic organization and integration of complex interactions taking place within various biological pathways. Currently, the information of the biological pathways is dispersed in multiple databases in various formats. hiPathDB is an integrated pathway database that combines the curated human pathway data of NCI-Nature PID, Reactome, BioCarta and KEGG. In total, it includes 1661 pathways consisting of 8976 distinct physical entities.

hiPathDB provides two different types of integration. The pathway-level integration, conceptually a simple collection of individual pathways, was achieved by devising an elaborate model that takes distinct features of four databases into account and subsequently reformatting all pathways in accordance with our model. The entity-level integration creates a single unified pathway that encompasses all pathways by merging common components. Even though the detailed molecular-level information such as complex formation or post-translational modifications tends to be lost, such integration makes it possible to investigate signaling network over the entire pathways and allows identification of pathway cross-talks. Another strong merit of hiPathDB is the built-in pathway visualization module that supports explorative studies of complex networks in an interactive fashion. The layout algorithm is optimized for virtually automatic visualization of the pathways. hiPathDB is available at http://hiPathDB.kobic.re.kr.

"Antagonistic regulation of transmembrane 4 L6 family member 5 attenuates fibrotic phenotypes in CCl(4) -treated mice."

Kang, M., S. J. Jeong, S. Y. Park, H. J. Lee, H. J. Kim, K. H. Park, S. K. Ye, S. H. Kim and J. W. Lee (2012). FEBS J 279(4): 625-635.

The development of liver fibrosis from chronic inflammation can involve epithelial-mesenchymal transition (EMT). Severe liver fibrosis can progress to cirrhosis, and further to hepatocellular carcinoma. Because the tetraspanin transmembrane 4 L6 family member 5 (TM4SF5) induces EMT and is highly expressed in hepatocellular carcinoma, it is of interest to investigate whether TM4SF5 expression is correlated with EMT processes during the development of fibrotic liver features. Using hepatic cells in vitro and a CCl(4) -mediated mouse liver in vivo model, we examined whether TM4SF5 is expressed during liver fibrosis mediated by CCl(4) administration and whether treatment with anti-TM4SF5 reagent blocks the fibrotic liver features. Here, we found that TM4SF5 expression was induced by the transforming growth factor (TGF)beta1 and epidermal growth factor signaling pathways in hepatocytes in vitro. In the CCl(4) -mediated mouse liver model, TM4SF5 was expressed during the liver fibrosis mediated by CCl(4) administration and correlated with alpha-smooth muscleactin expression, collagen I deposition, and TGFbeta1 and epidermal growth factor receptor signaling activation in fibrotic septa regions. Interestingly, treatment with anti-TM4SF5 reagent blocked the TM4SF5-mediated liver fibrotic features: the formationof fibrotic septa with alpha-smooth muscle actin expression and collagen I deposition was attenuated by treatment with anti-TM4SF5 reagent. These results suggest that TM4SF5 expression mediated by TGFbeta1 and growth factor can facilitate fibrotic processes during chronic liver injuries. TM4SF5 is thus a candidate target for prevention of liver fibrosis following chronic liver injury.

"Bilateral inhibition of HAUSP deubiquitinase by a viral interferon regulatory factor protein."

Lee, H. R., W. C. Choi, S. Lee, J. Hwang, E. Hwang, K. Guchhait, J. Haas, Z. Toth, Y. H. Jeon, T. K. Oh, M. H. Kim and J. U. Jung (2011). Nat Struct Mol Biol 18(12): 1336-1344.

Herpesvirus-associated ubiquitin-specific protease (HAUSP) regulates the stability of p53 and the p53-binding protein MDM2, implicating HAUSP as a therapeutic target for tuning p53-mediated antitumor activity. Here we report the structural analysis of HAUSP with Kaposi's sarcoma-associated herpesvirus viral interferon (IFN) regulatory factor 4 (vIRF4) and the discovery of two vIRF4-derived peptides, vif1 and vif2, as potent and selective HAUSP antagonists. This analysis reveals a bilateral belt-type interaction that results in inhibition of HAUSP. The vif1 peptide binds the HAUSP TRAF domain, competitively blocking substrate binding, whereas the vif2 peptide binds both the HAUSP TRAF and catalytic domains, robustly suppressing its deubiquitination activity. Peptide treatments comprehensively blocked HAUSP, leading to p53-dependent cell-cycle arrest and apoptosis in culture and to tumor regression in xenograft mouse model. Thus, the virus has developed a unique strategy to target the HAUSP-MDM2-p53 pathway, and these virus-derived short peptides represent biologically active HAUSP antagonists.

"Targeted disruption of Mcm10 causes defective embryonic cell proliferation and early embryo lethality."

Lim, H. J., Y. Jeon, C. H. Jeon, J. H. Kim and H. Lee (2011). Biochim Biophys Acta 1813(10): 1777-1783.

Minichromosome maintenance 10 (MCM10) is a conserved, abundant nuclear protein, which plays a key role in the initiation of eukaryotic chromosomal DNA replication and elongation. To elucidate the physiological importance of MCM10 in vivo, we generated conventional knockout mice.No MCM10-null embryos were recovered after E8.5, and the mutation was found to be lethal before the implantation stage. Mutant embryos showed apparently normal growth until the morula stage, but growth defects after this stage. The dramatic reduction of 5-bromo-2-deoxyuridine (BrdU) incorporation in the mutant embryo, followed by cell death, suggests that defective cell proliferation may underlie this developmental failure. Taken together, these findings provide the first unequivocal genetic evidence for an essential and non-redundant physiological role of MCM10 during murine peri-implantation development.

"Determination of UV-induced DNA damages to suppress protein expression using reporter gene assay-based single cell cotransfection imaging cytometry."

Tak, Y. K., W. Y. Kim, E. Han, M. J. Kim, J. A. Kim, C. Y. Lim and J. M. Song (2011). Toxicol Lett 204(1): 25-31.

Effects of UVB or UVC-induced DNA damage were simultaneously monitored at single cellular level by analyzing the change of yellow fluorescent protein (YFP) and red fluorescent protein (RFP) expression in human embryonic kidney (HEK) 293 cells using multicolor single-cell imaging cytometry. The method is based on the idea that there exists a quantitative correlation between the degree of UV-induced DNA damage and protein expression. A cotransfection assay was performed using UVB irradiated YFP and UVC irradiated RFP genes to eliminate cell-to-cell variation in protein expression yield. Up to an UVB irradiation dose of 50kJ/m(2), YFP expression yield did not change compared to control. On the other hand, RFP expression yield decreased remarkably asthe UVC dose increased from 79.5 to 159J/m(2). The results showed that a certain level of DNA damage is efficiently repaired by intracellular repair mechanism and does not influence protein mutation. In addition, it was found that the amount of DNA damageinduced by UVB in sunlight would not interfere with normal protein expression in the human body. Single-cell imaging cytometry is a cell lysis-free approach to directly monitor the intracellular correlation between the degree of UV-induced DNA damage and protein expression.

"Structural and functional characterization of Helicobacter pylori DsbG."

Yoon, J. Y., J. Kim, S. J. Lee, H. S. Kim, H. N. Im, H. J. Yoon, K. H. Kim, S. J. Kim, B. W. Han and S. W. Suh (2011). FEBS Lett 585(24): 3862-3867.

Dsb proteins play important roles in bacterial pathogenicity. To better understand the role of Dsb proteins in Helicobacter pylori, we have structurally and functionally characterized H. pylori DsbG (HP0231). The monomer consists of two domains connected by a helical linker. Two monomers associate to form a V-shaped dimer. The monomeric and dimeric structures of H. pylori DsbG show significant differences compared to Escherichia coli DsbG. Two polyethylene glycol molecules are bound in the cleft of the V-shaped dimer, suggesting a possible role as a chaperone. Furthermore, we show that H. pylori DsbG functions as a reductase against HP0518, a putative L,D-transpeptidase with a catalytic cysteine residue.

"One target, different effects: a comparison of distinct therapeutic antibodies against the same targets."

Shim, H. (2011). Exp Mol Med 43(10): 539-549.

To date, more than 30 antibodies have been approved worldwide for therapeutic use. While the monoclonal antibody market is rapidly growing, the clinical use of therapeutic antibodies is mostly limited to treatment of cancers and immunological disorders. Moreover,antibodies against only five targets (TNF-alpha, HER2, CD20, EGFR, and VEGF) account for more than 80 percent of the worldwide market of therapeutic antibodies. The shortage of novel, clinically proven targets has resulted in the development of many distinct therapeutic antibodies against a small number of proven targets, based on the premise that different antibody molecules against the same target antigen have distinct biological and clinical effects from one another. For example, four antibodies againstTNF-alpha have been approved by the FDA -- infliximab, adalimumab, golimumab, and certolizumab pegol -- with many more in clinical and preclinical development. The situation is similar for HER2, CD20, EGFR, and VEGF, each having one or more approved antibodies and many more under development. This review discusses the different binding characteristics, mechanisms of action, and biological and clinical activities of multiple monoclonal antibodies against TNF-alpha, HER-2, CD20, and EGFR and provides insights into the development of therapeutic antibodies.

"High-content screening of drug-induced cardiotoxicity using quantitative single cell imaging cytometry on microfluidic device."

Kim, M. J., S. C. Lee, S. Pal, E. Han and J. M. Song (2011). Lab Chip 11(1): 104-114.

Drug-induced cardiotoxicity or cytotoxicity followed by cell death in cardiac muscle is one of the major concerns in drug development. Herein, we report a high-content quantitative multicolor single cell imaging tool for automatic screening of drug-induced cardiotoxicity in an intact cell. A tunable multicolor imaging system coupled with a miniaturized sample platform was destined to elucidate drug-induced cardiotoxicity via simultaneous quantitative monitoring of intracellular sodium ion concentration, potassium ion channel

permeability and apoptosis/necrosis in H9c2(2-1) cell line. Cells were treated with cisapride (a human ether-a-go-go-related gene (hERG) channel blocker), digoxin (Na(+)/K(+)-pump blocker), camptothecin (anticancer agent) and a newly synthesized anti-cancer drug candidate (SH-03). Decrease in potassium channel permeability in cisapride-treated cells indicated that it can also inhibit the trafficking of the hERG channel. Digoxin treatment resulted in an increase of intracellular [Na(+)]. However, it did not affect potassium channel permeability. Camptothecin and SH-03 did not show any cytotoxic effect at normal use (</=300 nM and 10 muM, respectively). This result clearly indicates the potential of SH-03 as a new anticancer drug candidate. The developed method was also used to correlate the cell death pathway with alterations in intracellular [Na(+)]. The developed protocol can directly depict and quantitate targeted cellular responses, subsequently enabling an automated,easy to operate tool that is applicable to drug-induced cytotoxicity monitoring with special reference to next generation drug discovery screening. This multicolor imaging based system has great potential as a complementary system to the conventional patch clamp technique and flow cytometric measurement for the screening of drug cardiotoxicity.

"Solution structure of the Zbeta domain of human DNA-dependent activator of IFN-regulatory factors and its binding modes to B- and Z-DNAs."

Kim, K., B. I. Khayrutdinov, C. K. Lee, H. K. Cheong, S. W. Kang, H. Park, S. Lee, Y. G. Kim, J. Jee, A. Rich, K. K. Kim and Y. H. Jeon (2011). Proc Natl Acad Sci U S A 108(17): 6921-6926.

The DNA-dependent activator of IFN-regulatory factors (DAI), also known as DLM-1/ZBP1, initiates an innate immune response by binding to foreign DNAs in the cytosol. For full activation of the immune response, three DNA binding domains at the N terminus are required: two Z-DNA binding domains (ZBDs), Zalpha and Zbeta, and an adjacent putative B-DNA binding domain. The crystal structure of the Zbeta domain of human DAI (hZbeta(DAI)) in complex with Z-DNA revealed structural features distinct from other known Z-DNA binding proteins, and it was classified as a group II ZBD. To gain structural insights into the DNA binding mechanism of hZbeta(DAI), the solution structure of the free hZbeta(DAI) was solved, and its bindings to B- and Z-DNAs were analyzed by NMR spectroscopy. Compared to the Z-DNA-bound structure, the conformation of free hZbeta(DAI) has notable alterations in the alpha3 recognition helix, the "wing," and Y145, which are critical in Z-DNA recognition. Unlike some other Zalpha domains, hZbeta(DAI) appears to have conformational flexibility, and structural adaptation is required for Z-DNA binding. Chemical-shift perturbation experiments revealed that hZbeta(DAI) also binds weakly to B-DNA via a different binding mode. The C-terminal domain of DAI is reported to undergo a conformational change on B-DNA binding; thus, it is possible that these changes are correlated. During the innate immune response, hZbeta(DAI) is likely to play an active role in binding to DNAs in both B and Z conformations in the recognition of foreign DNAs.

"Metformin represses self-renewal of the human breast carcinoma stem cells via inhibition of estrogen receptor-mediated OCT4 expression."

Jung, J. W., S. B. Park, S. J. Lee, M. S. Seo, J. E. Trosko and K. S. Kang (2011). PLoS One 6(11): e28068.

Metformin, a Type II diabetic treatment drug, which inhibits transcription of gluconeogenesis genes, has

recently been shown to lower the risk of some diabetes-related tumors, including breast cancer. Recently, "cancer stem cells" have been demonstrated to sustain the growth of tumors and are resistant to therapy. To test the hypothesis that metformin might be reducing the risk to breast cancers, the human breast carcinoma cell line, MCF-7, grown in 3-dimensional mammospheres which represent human breast cancer stem cell population, were treated with various known and suspected breast cancer chemicals with and without non-cytotoxic concentrations of metformin. Using OCT4 expression as a marker for the cancer stem cells, the number and size were measured in these cells. Results demonstrated that TCDD (100 nM) and bisphenol A (10 microM) increased the number and size of the mammospheres, as did estrogen (10 nM E2). By monitoring a cancer stem cell marker, OCT4, the stimulation by these chemicals was correlated with the increased expression of OCT4. On the other hand, metformin at 1 and 10 mM concentration dramatically reduced the size and number of mammospheres. Results also demonstrated the metformin reduced the expression of OCT4 in E2 & TCDD mammospheres but not in the bisphenol A mammospheres, suggesting different mechanisms of action of the bisphenol A on human breast carcinoma cells. In addition, these results support the use of 3-dimensional human breast cancer stem cells as a means to screen for potential human breast tumor promoters and breast chemopreventive and chemotherapeutic agents.

"Entamoeba lysyl-tRNA synthetase contains a cytokine-like domain with chemokine activity towards human endothelial cells."

Castro de Moura, M., F. Miro, J. M. Han, S. Kim, A. Celada and L. Ribas de Pouplana (2011). PLoS Negl Trop Dis 5(11): e1398.

Immunological pressure encountered by protozoan parasites drives the selection of strategies to modulate or avoid the immune responses of their hosts. Here we show that the parasite Entamoeba histolytica has evolved a chemokine that mimics the sequence, structure, and function of the human cytokine HsEMAPII (Homo sapiens endothelial monocyte activating polypeptide II). This Entamoeba EMAPII-like polypeptide (EELP) is translated as a domain attached to two different aminoacyl-tRNA synthetases (aaRS) that areoverexpressed when parasites are exposed to inflammatory signals. EELP is dispensable for the tRNA aminoacylation activity of the enzymes that harbor it, and it is cleaved from them by Entamoeba proteases to generate a standalone cytokine. Isolated EELP acts as a chemoattractant for human cells, but its cell specificity is different from that of HsEMAPII. We show that cell specificity differences between HsEMAPII and EELP can be swapped by site directed mutagenesis of only two residues in the cytokines' signal sequence. Thus, Entamoeba has evolved a functional mimic of an aaRS-associated human cytokine with modified cell specificity.

"Importin beta plays an essential role in the regulation of the LysRS-Ap(4)A pathway in immunologically activated mast cells."

Carmi-Levy, I., A. Motzik, Y. Ofir-Birin, Z. Yagil, C. M. Yang, D. M. Kemeny, J. M. Han, S. Kim, G. Kay, H. Nechushtan, R. Suzuki, J. Rivera and E. Razin (2011). Mol Cell Biol 31(10): 2111-2121.

We recently reported that diadenosine tetraphosphate hydrolase (Ap(4)A hydrolase) plays a critical role in gene expression via regulation of intracellular Ap(4)A levels. This enzyme serves as a component of our newly described lysyl tRNA synthetase (LysRS)-Ap(4)A biochemical pathway that is triggered upon immunological

challenge. Here we explored the mechanism of this enzyme's translocation into the nucleus and found its immunologically dependent association with importin beta. Silencing of importin betaprevented Ap(4)A hydrolase nuclear translocation and affected the local concentration of Ap(4)A, which led to an increase in microphthalmia transcription factor (MITF) transcriptional activity. Furthermore, immunological activation of mast cells resulted in dephosphorylation of Ap(4)A hydrolase, which changed the hydrolytic activity of the enzyme.

"Dual role of methionyl-tRNA synthetase in the regulation of translation and tumor suppressor activity of aminoacyl-tRNA synthetase-interacting multifunctional protein-3."

Kwon, N. H., T. Kang, J. Y. Lee, H. H. Kim, H. R. Kim, J. Hong, Y. S. Oh, J. M. Han, M. J. Ku, S. Y. Lee and S. Kim (2011). Proc Natl Acad Sci U S A 108(49): 19635-19640.

Mammalian methionyl-tRNA synthetase (MRS) plays an essential role in initiating translation by transferring Met to initiator tRNA (tRNA(i)(Met)). MRS also provides a cytosolic anchoring site for aminoacyl-tRNA synthetase-interacting multifunctional protein-3 (AIMP3)/p18, a potent tumor suppressor that is translocated to the nucleus for DNA repair upon DNA damage. However, the mechanism by which this enzyme mediates these two seemingly unrelated functions is unknown. Here we demonstrate that AIMP3 is released from MRS by UV irradiation-induced stress. Dissociation was induced by phosphorylation of MRS at Ser662 by general control nonrepressed-2 (GCN2) following UV irradiation. Substitution of Ser662 to Asp (S662D) induced a conformational change in MRS and significantly reduced its interaction with AIMP3. This mutant possessed significantlyreduced MRS catalytic activity because of loss of tRNA(Met) binding, resulting in down-regulation of global translation. According to the Met incorporation assay using stable HeLa cells expressing MRS S662A or eukaryotic initiation factor-2 subunit-alpha (eIF2alpha) S51A, inactivation of GCN2-induced phosphorylation at eIF2alpha or MRS augmented the role of the other, suggesting a cross-talk between MRS and eIF2alpha for efficient translational inhibition. This work reveals a unique mode of regulation of global translation as mediated by aminoacyl-tRNA synthetase, specifically MRS, which we herein identified as a previously unidentified GCN2 substrate. In addition, our research suggests a dual role for MRS: (i) as a coregulator with eIF2alpha for GCN2-mediated translational inhibition; and (ii) as a coupler of translational inhibition and DNA repair following DNA damage by

"Survival and Differentiation of Mammary Epithelial Cells in Mammary Gland Development Require Nuclear Retention of Id2 Due to Rank Signaling."

Kim, N. S., H. T. Kim, M. C. Kwon, S. W. Choi, Y. Y. Kim, K. J. Yoon, B. K. Koo, M. P. Kong, J. Shin, Y. Cho and Y. Y. Kong (2011). Mol Cell Biol 31(23): 4775-4788.

RANKL plays an essential role in mammary gland development during pregnancy. However, the molecular mechanism by which RANK signaling leads to mammary gland development is largely unknown. We report here that RANKL stimulation induces phosphorylation of Id2 at serine 5, which leads to nuclear retention of Id2. In lactating Id2Tg; RANKL(-/-) mice, Id2 was not phosphorylated and was localized in the cytoplasm. In

addition, in lactating Id2(S5A)Tg mice, Id2(S5A) (with serine 5 mutated to alanine) was exclusively localized in the cytoplasm of mammary epithelial cells (MECs), while endogenous Id2 was localized in the nucleus. Intriguingly, nuclear expression of Id2(S5A) rescued increased apoptosis and defective differentiation of MECs in RANKL(-/-) mice. Our results demonstrate that nuclear retention of Id2 due to RANK signaling plays a decisive role in the survival and differentiation of MECs during mammary gland development.
releasing bound tumor suppressor AIMP3 for its nuclear translocation.

"Overexpression, crystallization and preliminary X-ray crystallographic analysis of the C-terminal cytosolic domain of mouse anoctamin 1."

Park, S. H., H. K. Chung, J. Kim do, M. R. Han, M. S. Park, U. Oh, H. J. Kim and B. W. Han (2011). Acta Crystallogr Sect F Struct Biol Cryst Commun 67(Pt 10): 1250-1252.

Transmembrane protein 16A (TMEM16A, also known as anoctamin 1; ANO1) is a bona fide Ca(2+)-activated chloride channel that is activated by intracellular Ca(2+)- and Ca(2+)-mobilizing stimuli and plays important roles in a variety of physiological functions. To elucidate the structural features of ANO1, structural analysis of the C-terminal cytosolic domain of mouse ANO1 (mANO1-CTD) was initiated. mANO1-CTD was overexpressed in Escherichia coli and was crystallized at 297 K using a reservoir solution consisting of 0.2 M sodium acetate trihydrate, 0.1 M Tris-HCl pH 8.5 and 30%(w/v) PEG 4000. X-ray diffraction data were collected to 2.3 A resolution. The crystals belonged to the orthorhombic space group P2(1)2(1)2(1), with unit-cell parameters a = 73.96, b = 103.73, c = 114.71 A. If it is assumed that eight copies of a monomer moleculeare present in the crystallographic asymmetric unit, the crystal volume per protein mass (V(M)) is 2.38 A(3) Da(-1) and the solvent content is 48.38%. Attempts to solve the structure of mANO1-CTD by the MAD method using selenomethionine-labelled mANO1-CTD or heavy-atom-derivatized crystals are in progress.

"Enhancement of toll-like receptor 2-mediated immune responses by AIMP1, a novel cytokine, in mouse dendritic cells."

Kim, E., H. J. Hong, D. Cho, J. M. Han, S. Kim and T. S. Kim (2011). Immunology 134(1): 73-81.

Aminoacyl tRNA synthetase-interacting protein 1 (AIMP1) is a novel pleiotropic cytokine that was identified initially from Meth A-induced fibrosarcoma. It is expressed in the salivary glands, small intestine and large intestine, and is associated with the innate immune system. Previously, we demonstrated that AIMP1 might function as a regulator of innate immune responses by inducing the maturation and activationof bone-marrow-derived dendritic cells (BM-DCs). Toll-like receptors (TLRs) are major pathogen-recognition receptors that are constitutively expressed on DCs. In this study, we attempted to determine whether AIMP1 is capable of regulating the expression of TLRs, and also capable of affecting the TLR-mediated activation of DCs. Expression of TLR1, -2, -3 and -7 was highly induced by AIMP1 treatment in BM-DCs, whereas the expression of other TLRs was either down-regulated or remained unchanged. In particular, the expression of the TLR2 protein was up-regulated by AIMP1 in a time-dependent and dose-dependent manner, and was suppressed upon the addition of BAY11-7082, an inhibitor of nuclear factor-kappaB. AIMP1 was also shown to increase nuclear factor-kappaB binding activity. Importantly, AIMP1 enhanced the production of interleukin-6 and interleukin-12, and the expression of co-stimulatory molecules on BM-DCs when combined with lipoteichoic acid or Pam3Cys, two well-known TLR2 agonists. Collectively, these results demonstrate that the AIMP1 protein enhances TLR2-mediated immune responses via the up-regulation of TLR2 expression.

"Cancer-associated splicing variant of tumor suppressor AIMP2/p38: pathological implication in tumorigenesis."

Choi, J. W., D. G. Kim, A. E. Lee, H. R. Kim, J. Y. Lee, N. H. Kwon, Y. K. Shin, S. K. Hwang, S. H. Chang, M. H. Cho, Y. L. Choi, J. Kim, S. H. Oh, B. Kim, S. Y. Kim, H. S. Jeon, J. Y. Park, H. P. Kang, B. J. Park, J. M. Han and S. Kim (2011). PLoS Genet 7(3): e1001351.

Although ARS-interacting multifunctional protein 2 (AIMP2, also named as MSC p38) was first found as a component for a macromolecular tRNA synthetase complex, it wasrecently discovered to dissociate from the complex and work as a potent tumor suppressor. Upon DNA damage, AIMP2 promotes apoptosis through the protective interaction with p53. However, it was not demonstrated whether AIMP2 was indeed pathologically linked to human cancer. In this work, we found that a splicing variant of AIMP2 lacking exon 2 (AIMP2-DX2) is highly expressed by alternative splicing in human lung cancer cells and patient's tissues. AIMP2-DX2 compromised pro-apoptotic activity of normal AIMP2through the competitive binding to p53. The cells with higher level of AIMP2-DX2 showed higher propensity to form anchorage-independent colonies and increased resistance to cell death. Mice constitutively expressing this variant showed increased susceptibility to carcinogen-induced lung tumorigenesis. The expression ratio of AIMP2-DX2 to normal AIMP2 was increased according to lung cancer stage and showed a positive correlation with the survival of patients. Thus, this work identified an oncogenic splicing variant of a tumor suppressor, AIMP2/p38, and suggests its potential for anti-cancer target.

"Aminoacyl-tRNA synthetases and tumorigenesis: more than housekeeping."

Kim, S., S. You and D. Hwang (2011). Nat Rev Cancer 11(10): 708-718.

Over the past decade, the identification of cancer-associated factors has been a subject of primary interest not only for understanding the basic mechanisms of tumorigenesis but also for discovering the associated therapeutic targets. However, aminoacyl-tRNA synthetases (ARSs) have been overlooked, mostly because many assumed that they were simply 'housekeepers' that were involved in protein synthesis. Mammalian ARSs have evolved many additional domains that are not necessarily linked to their catalytic activities. With these domains, they interact with diverse regulatory factors. In addition, the expression of some ARSs is dynamically changed depending on various cellular types and stresses. This Analysis article addresses the potential pathophysiological implications of ARSs in tumorigenesis.

"GARNET-gene set analysis with exploration of annotation relations."

Rho, K., B. Kim, Y. Jang, S. Lee, T. Bae, J. Seo, C. Seo, J. Lee, H. Kang, U. Yu, S. Kim and W. K. Kim (2011). BMC Bioinformatics 12 Suppl 1: S25.

BACKGROUND: Gene set analysis is a powerful method of deducing biological meaning for ana priori defined set of genes. Numerous tools have been developed to test statistical enrichment or depletion in specific pathways or gene ontology (GO) terms. Major difficulties towards biological interpretation are integrating diverse types of annotation categories and exploring the relationships between annotation terms of similar information. RESULTS: GARNET (Gene Annotation Relationship NEtwork Tools) is an integrative platform for gene set analysis with many novel features. It includes tools for retrieval of genes from annotation database, statistical analysis & visualization of annotation relationships, and managing gene sets. In an effort to allow access to a full spectrum of amassed biological knowledge, we have integrated a variety of annotation data that include the GO, domain, disease, drug, chromosomal location, and custom-defined annotations. Diverse types of molecular networks (pathways, transcription and microRNA regulations, protein-protein interaction) are also included. The pair-wise relationship between annotation gene sets was calculated using kappa statistics. GARNET consists of three modules--gene set manager, gene set analysis and gene set retrieval, which are tightly integrated to provide virtually automatic analysis for gene sets. A dedicated viewer for annotation network has been developed to facilitate exploration of the related annotations. CONCLUSIONS: GARNET (gene annotation relationship network tools) is an integrative platform for diverse types of gene set analysis, where complex relationships among gene annotations can be easily explored with an intuitive network visualization tool (http://garnet.isysbio.org/ or http://ercsb.ewha.ac.kr/garnet/).

"Crystal structure of Arabidopsis thaliana 12-oxophytodienoate reductase isoform 3 in complex with 8-iso prostaglandin A(1)."

Han, B. W., T. E. Malone, J. Kim do, C. A. Bingman, H. J. Kim, B. G. Fox and G. N. Phillips, Jr. (2011). Proteins 79(11): 3236-3241.

12-Oxophytodienoate reductase 3 (OPR3), one of the enzymes involved in the biosynthesis of the plant hormone jasmonic acid (JA), catalyzes the reduction of the cyclopentenone ring of (9S,13S)-12-oxophytodienoate [(9S,13S)-OPDA]. However, there has been no structural information about the interaction between OPRs and the physiologically relevant (9S,13S)-OPDA. Here we report the crystal structure of Arabidopsis thaliana OPR3 in complex with 8-iso prostaglandin A1 (8-iso PGA1) which has the same stereochemistry in the cyclopentenone ring as in the physiologically relevant 9S,13S-OPDA. This structure reveals a new binding mode for substrate that likely contributes to the relaxed stereospecificity observed for AtOPR3.

"VEGF inhibitor (Iressa) arrests histone deacetylase expression: single-cell cotransfection imaging cytometry for multi-target-multi-drug analysis."

Tak, Y. K., P. K. Naoghare, E. Han and J. M. Song (2011). J Cell Physiol 226(8): 2115-2122.

Multi-target-multi-drug approaches are needed to accelerate the process of drug discovery screening and to design efficient therapeutic strategies against diseases that involve alterations in multiplecellular targets. Herein we report single-cell cotransfection imaging cytometry to quantitatively screen drug-induced off-target effects. Vascular endothelial growth factor (VEGF) and histone deacetylase (HDAC) genes amplified from the genomic DNA were cloned in fluorescently tagged gene constructs (RFP-HDAC/YFP-VEGF). These gene constructs were cotransfected in HEK-293 cells to explore the possibility of off-target effects of

4-phenylbutyrate and Iressa on the expression of VEGF and HDAC through single-cell imaging cytometry. Iressa (10 microM) treatment at the time of cotransfection or 48 h after cotransfection of RFP-HDAC/YFP-VEGF plasmids in HEK-293 cells resulted in off-target effects on HDAC expression. These results suggest possible applications of Iressa in the treatment of diseases in which expression of both HDAC and VEGF should be inhibited. 4-Phenylbutyrate (2.0 mM) did not show any off-target effects on VEGF expression. The developed quantitative multicolor live single-cell cotransfection imaging can be employed to select better drug combinations for faster screening and greater accuracy in multi-target-multi-drug analysis by increasing the on-target/desired off-target effects and eliminating the undesirable off-target effects.

"Benzothiazole-containing hydroxamic acids as histone deacetylase inhibitors and antitumor agents."

Oanh, D. T., H. V. Hai, S. H. Park, H. J. Kim, B. W. Han, H. S. Kim, J. T. Hong, S. B. Han, V. T. Hue and N. H. Nam (2011). Bioorg Med Chem Lett 21(24): 7509-7512.

Data from clinical studies indicate that inhibitors of Class I and Class II histone deacetylase (HDAC) enzymes show great promise for the treatment of cancer. Zolinza (SAHA, Zolinza) was recently approved by the FDA for the treatment of the cutaneous manifestations of cutaneous T-cell lymphoma. As a part of our ongoing effort to identify novel small molecules to target these important enzymes, we have prepared two series of benzothiazole-containing analogues of SAHA. It was found that several compounds with 6C-bridge linking benzothiazole moiety and hydroxamic functional groups showed good inhibition against HDAC3 and 4 at as low as 1 mug/ml and exhibited potent cytotoxicity against five cancer cell lines with average IC(50) values of as low as 0.81 mug/ml, almost equipotent to SAHA.

"In situ fabrication and actuation of polymer magnetic microstructures."

Chung, S. E., J. Kim, S. E. Choi, L. N. Kim and S. Kwon (2011). Journal of Microelectromechanical Systems 20(4): 785-787.

We demonstrate a single-exposure in situ magnetic actuator fabrication technique using magnetic nanoparticles (MNs) containing UV curable polymer in a Polydimethylsiloxane (PDMS) channel. Microstructures with a 3-D anchored cantilever as well as free-floating components are fabricated in a single step at a single site without the use of a sacrificial layer. By controlling the location of high oxygen concentration area through PDMS substrate patterning, we can create partially bound and free-floating movement-restricted structures. This allows us to create complex magnetic actuators, such as a 3-D anchored cantilever, motor type, and rail-guided magnetic actuators. The actuating performance of UV photopatterned magnetic microstructures depends on the MN concentration in photopolymer resin and magnetic field intensity. The measured translational velocity of magnetic microactuators with a 1 : 10 MN concentration is 140 mu m/s under 1400 G of magnetic field in poly(ethylene glycol) diacrylate resin. Also, we demonstrate selective magnetic actuation of heterogeneous structures composed of magnetic and nonmagnetic parts self-assembled in railed microfluidic channels. Only magnetic parts from the assembly selectively actuated due to the magnetic field without response to the flow. Therefore, we have developed a versatile magnetic microstructure fabrication method that is very simple and fast, enabling rapid in situ fabrication and actuation.

"Sphingosylphosphorylcholine attenuated β-amyloid production by reducing BACE1 expression and catalysis in PC12 cells."

Yi, H., S. J. Lee, J. Lee, C. S. Myung, W. K. Park, H. J. Lim, G. H. Lee, J. Y. Kong and H. Cho (2011). Neurochem Res 36(11): 2083-2090.

Abnormal accumulation of beta-amyloid (Abeta) is the main characteristic of Alzheimer's disease (AD) brain and Abeta peptides are generated from proteolytic cleavages of amyloid precursor protein (APP) by beta-site APP-converting enzyme 1 (BACE1) and presenilin 1 (PS1). Sphingosylphosphorylcholine (SPC), a choline-containing sphingolipid, showed suppressive effect on Abeta production in PC12 cells which stably express Swedish mutant of amyloid precursor protein (APPsw). SPC (> 3 muM) significantly lowered the accumulation of Abeta40/42 and the expression of BACE1. However, the transcriptions of other APP processing enzymes like ADAM10 and PS1 were not affected by the SPC addition. Meanwhile, phosphocholine (PC) or other lysophospholipids, such as lysophosphatidylcholine (LPC), lysophosphatidic acid (LPA), sphingosyl-1-phosphate (S1P), did not alter BACE1 expression. Down-regulatory effect of SPC on BACE1 expression appeared to be mediated by NF-kappaB which is known to suppress the trans-activation of BACE1 promoter in PC12 cells. Here, the nuclear tanslocation of NF-kappaB was enhanced by SPC treatment in immune-fluorescent image analysis and NF-kappaB reporter assay. Furthermore, the catalytic activities of BACE1 and BACE2 were dose-dependently inhibited by SPC displaying IC(5)(0) values of 2.79 muM and 12.05 muM, respectively. Overall, these data suggest that SPC has the potential to ameliorate Abeta pathology in neurons by down-regulating the BACE1-mediated amyloidogenic pathway.

"Polymer based chemical delivery to multichannel capillary patterned cells."

Lee, S. H., A. J. Heinz, S. E. Choi, W. Park and S. Kwon (2011). Lab Chip 11(4): 605-608.

In order to match the controllability of traditional pipetting with the advantages of microfluidics, we introduce the concept of polymer based chemical delivery to multichannel capillary patterned cells. Here we demonstrate that UV polymerized hydrogel can be used as a miniature pipet to deliver picolitre chemical quantities to multichannel capillary patterned cells.

"Crystal structure of human Mre11: understanding tumorigenic mutations."

Park, Y. B., J. Chae, Y. C. Kim and Y. Cho (2011). Structure 19(11): 1591-1602.

Mre11 plays an important role in repairing damaged DNA by cleaving broken ends and by providing a platform for other DNA repair proteins. Various Mre11 mutations have been identified in several types of cancer. We have determined the crystal structure of the human Mre11 core (hMre11), which contains the nuclease and capping domains. hMre11 dimerizes through the interfaces between loop beta3-alpha3 from one Mre11 and loop beta4-beta5 from another Mre11, and between loop alpha2-beta3 from one Mre11 and helices alpha2 and alpha3 from another Mre11, and assembles into a completely different dimeric architecture

compared with bacterial or archaeal Mre11 homologs. Nbs1 binds to the region containing loop alpha2-beta3 which participates in dimerization. The hMre11 structure in conjunction with biochemical analyses reveals that many tumorigenic mutations are primarily associated with Nbs1 binding and partly with nuclease activities, providing a framework for understanding how mutations inactivate Mre11.

"Crystal structure of the Mre11-Rad50-ATPγS complex: understanding the interplay between Mre11 and Rad50."

Lim, H. S., J. S. Kim, Y. B. Park, G. H. Gwon and Y. Cho (2011). Genes Dev 25(10): 1091-1104.

Communication between Mre11 and Rad50 in the MR complex is critical for the sensing, damage signaling, and repair of DNA double-strand breaks. To understand the basis for interregulation between Mre11 and Rad50, we determined the crystal structure of the Mre11-Rad50-ATPgammaS complex. Mre11 brings the two Rad50 molecules into close proximity and promotes ATPase activity by (1) holding the coiled-coil arm of Rad50 through its C-terminal domain, (2) stabilizing the signature motif and P loop of Rad50 via its capping domain, and (3) forming a dimer through the nuclease domain. ATP-bound Rad50 negatively regulates the nuclease activity of Mre11 by blocking the active site of Mre11. Hydrolysis of ATP disengages Rad50 molecules, and, concomitantly, the flexible linker that connects the C-terminal domain and the capping domain of Mre11 undergoes substantial conformational change to relocate Rad50 and unmask the active site of Mre11. Our structural and biochemical data provide insights into understanding the interplay between Mre11 and Rad50 to facilitate efficient DNA damage repair.

"TopBP1 deficiency causes an early embryonic lethality and induces cellular senescence in primary cells."

Jeon, Y., E. Ko, K. Y. Lee, M. J. Ko, S. Y. Park, J. Kang, C. H. Jeon, H. Lee and D. S. Hwang (2011). J Biol Chem 286(7): 5414-5422.

TopBP1 plays important roles in chromosome replication, DNA damage response, and other cellular regulatory functions in vertebrates. Although the roles of TopBP1 have been studied mostly in cancer cell lines, its physiological function remains unclear in mice and untransformed cells. We generated conditional knock-out mice in which exons 5 and 6 of the TopBP1 gene are flanked by loxP sequences. Although TopBP1-deficient embryos developed to the blastocyst stage, no homozygous mutant embryos were recovered at E8.5 or beyond, and completely resorbed embryos were frequent at E7.5, indicating that mutant embryos tend to die at the peri-implantation stage. This finding indicated that TopBP1 is essential for cell proliferation during early embryogenesis. Ablation of TopBP1 in TopBP1(flox/flox) mouse embryonic fibroblasts and 3T3 cells using Cre recombinase-expressing retrovirus arrests cell cycle progression at the G(1), S, and G(2)/M phases. The TopBP1-ablated mouse cells exhibit phosphorylation of H2AX and Chk2, indicating that the cells contain DNA breaks. The TopBP1-ablated mouse cells enter cellular senescence. Although RNA interference-mediated knockdown of TopBP1 induced cellular senescence in human primary cells, it induced apoptosis in cancer cells. Therefore, TopBP1 deficiency in untransformed mouse and human primary cells induces cellular senescence rather than apoptosis. These results indicate that TopBP1 is essential for cell proliferation and maintenance of chromosomal integrity.

"Programming magnetic anisotropy in polymeric microactuators."

Kim, J., S. E. Chung, S. E. Choi, H. Lee and S. Kwon (2011). Nat Mater 10(10): 747-752.

Polymeric microcomponents are widely used in microelectromechanical systems (MEMS) and lab-on-a-chip devices, but they suffer from the lack of complex motion, effective addressability and precise shape control. To address these needs, wefabricated polymeric nanocomposite microactuators driven by programmable heterogeneous magnetic anisotropy. Spatially modulated photopatterning was applied in a shape-independent manner to microactuator components by successive confinement of self-assembled magnetic nanoparticles in a fixed polymer matrix. By freely programming the rotational axis of each component, we demonstrate that the polymeric microactuators can undergo predesigned, complex two- and three-dimensional motion.

"Downregulation of lamin A by tumor suppressor AIMP3/p18 leads to a progeroid phenotype in mice."

Oh, Y. S., D. G. Kim, G. Kim, E. C. Choi, B. K. Kennedy, Y. Suh, B. J. Park and S. Kim (2010). Aging Cell 9(5): 810-822.

Although AIMP3/p18 is normally associated with the macromolecular tRNA synthetase complex, recent reports have revealed a new role of AIMP3 in tumor suppression. In this study, we generated a transgenic mouse that overexpresses AIMP3 and characterized the associated phenotype in vivo and in vitro. Surprisingly, the AIMP3 transgenic mouse exhibited a progeroid phenotype, and the cells that overexpressed AIMP3 showed accelerated senescence and defects in nuclear morphology. We found that overexpression of AIMP3 resulted in proteasome-dependent degradation of mature lamin A, but not of lamin C, prelamin A, or progerin. The resulting imbalance in the protein levels of lamin A isoforms, namely altered stoichiometry of prelamin A and progerin to lamin A, appeared to be responsible for a phenotype that resembled progeria. An increase in the level of endogenous AIMP3 has been observed in aged human tissues and cells. The findings in this report suggest that AIMP3 is a specific regulator of mature lamin A and imply that enhanced expression of AIMP3 might be a factor driving cellular and/or organismal aging.

"The hsSsu72 phosphatase is a cohesin-binding protein that regulates the resolution of sister chromatid arm cohesion."

Kim, H. S., K. H. Baek, G. H. Ha, J. C. Lee, Y. N. Kim, J. Lee, H. Y. Park, N. R. Lee, H. Lee, Y. Cho and C. W. Lee (2010). EMBO J 29(20): 3544-3557.

Cohesin is a multiprotein complex that establishes sister chromatid cohesion from S phase until mitosis or meiosis. In vertebrates, sister chromatid cohesion is dissolved in a stepwise manner: most cohesins are removed fromthe chromosome arms via a process that requires polo-like kinase 1 (Plk1), aurora B and Wapl, whereas a minor amount of cohesin, found preferentially at the centromere, is cleaved by separase following its activation by the anaphase-promoting complex/cyclosome. Here, we report that our budding yeast two-hybrid assay identified hsSsu72 phosphatase as a Rad21-binding protein. Additional experiments revealed

that Ssu72 directly interacts with Rad21 and SA2 in vitro and in vivo, and associates with sister chromatids in human cells. Interestingly, depletion or mutational inactivation of Ssu72 phosphatase activity caused the premature resolution of sister chromatid arm cohesion, whereas the overexpression of Ssu72 yielded high resistance to this resolution. Interestingly, it appears that Ssu72 regulates the cohesion of chromosome arms but not centromeres, and acts by counteracting the phosphorylation of SA2. Thus, our study provides important new evidence, suggesting that Ssu72 is a novel cohesin-binding protein capable of regulating cohesion between sister chromatid arms.

"DDS, 4,4'-diaminodiphenylsulfone, extends organismic lifespan."

Cho, S. C., M. C. Park, B. Keam, J. M. Choi, Y. Cho, S. Hyun, S. C. Park and J. Lee (2010). Proc Natl Acad Sci U S A 107(45): 19326-19331.

DDS, 4,4'-diaminodiphenylsulfone, is the most common drug prescribed to treat Hansen disease patients. In addition to its antibacterial activity, DDS has been reported to be involved in other cellular processes that occur in eukaryotic cells. Because DDS treatment significantly enhances the antioxidant activity in humans, we examined its effect on lifespan extension. Here we show that DDS extends organismic lifespan using Caenorhabditis elegans as a model system. DDS treatment caused a delay in aging and decreased the levels of a mitochondrial complex. The oxygen consumption rate was also significantly lowered. Consistent with these data, paraquat treatment evoked less reactiveoxygen species in DDS-treated worms, and these worms were less sensitive to paraquat. Interestingly enough, all of the molecular events caused by DDS treatment were consistently reproduced in mice treated with DDS for 3 mo and in the C2C12 muscle cell line. Structural prediction identified pyruvate kinase (PK) as a protein target of DDS. Indeed, DDS bound and inhibited PK in vitro and inhibited it in vivo, and a PK mutation conferred extended lifespan of C. elegans. Supplement of pyruvate to the media protected C2C12 cells from apoptosis caused by paraquat. Our findings establish the significance of DDS in lowering reactive oxygen species generation and extending the lifespan, which renders the rationale to examining the possible effect of DDS on human lifespan extension.

"Active guidance of 3D microstructures."

Lee, S. H., S. E. Choi, A. J. Heinz, W. Park, S. Han, Y. Jung and S. Kwon (2010). Small 6(23): 2668-2672.

A new method for sorting loaded microstructuresusing a platform known as active rail is presented. Active rail actively sorts grooved hydrogel microstructures at channel branch sites through pneumatic activation of a flexible rail. This paper provides a sorting mechanism that is capable of continuous flow reconfigurable multibranch guidance, and it demonstrates stacking of microstructures for combinatorial multicompartment chemical delivery.

2. Patents

No.	Application / Registration	Name	Applicant	Country	Date	Application / Registration No
1	Application	Crystal structure and crystallization of modified EPRS Protein	Sunghoon Kim	Rep. of Korea	20121218	1020120148212
2	Application	Direct preparation of functional insulin producing cell from human dermal fibroblasts	Kyung Sun Kang	Rep. of Korea	20121024	1020120118708
3	Application	METHOD FOR SCREENING AN AGENT PREVENTING OR TREATING CANCER USING GLYCYL-TRNA SYNTHETASE AND CADHERI	Sunghoon Kim	PCT	20121010	PCT/KR2012/008211
4	Application	PHARMACEUTICAL COMPOSITIOIN CONTAINING AMPK-ACTIVATING COMPOUND	Seung Bum Park	Rep. of Korea	20121005	1011901410000
5	Application	Novel use of leucyl tRNA synthetase	Sunghoon Kim	Rep. of Korea	20120924	1020120105694
6	Application	Novel use of leucyl tRNA synthetase	Sunghoon Kim	PCT	20120924	PCT/KR2012/007656
7	Application	Novel aniline derivatives and use thereof	Sunghoon Kim	Rep. of Korea	20120806	1020120085685
8	Application	Novel aniline derivatives and use thereof	Sunghoon Kim	PCT	20120806	PCT/KR2012/006238
9	Application	A novel TM4SF5 specific monoclonal antibody and use thereof	Jung Won Lee	Rep. of Korea	20120803	1020120085437
10	Application	Zinc finger library and engineered zinc finger protein screening using the same	Hyun Bo Shim	Rep. of Korea	20120731	1020120084182
11	Application	Method for crystallization of TRX-TXNIP complex mutein and 3D structure thereof	Myung Hee Kim	Rep. of Korea	20120712	10201200766310
12	Application	Pharmaceutical composition for the preventing or treating brain tumor or glioblastoma having resistance of Temodal containing Azathioprine as an active ingredient	Heeyeong Cho	Rep. of Korea	20120711	1020120075365
13	Application	Pharmaceutical composition for the preventing or treating brain tumor or glioblastoma having resistance of Temodal containing Benzydamine as an active ingredient	Heeyeong Cho	Rep. of Korea	20120711	1020120075364
14	Application	Method for preparing RNAi library	Byeong Jun Hwang	Rep. of Korea	20120704	1020120073003
15	Application	Method for preparing chimeric ribonucleic acid, cDNA and its derivatives	Byeong Jun Hwang	Rep. of Korea	20120704	1020120072944
16	Application	Method for screening anti-tumor agent	Ho Jun Seol	Rep. of Korea	20120702	1020120071889
17	Application	Method for Screening Anti-cancer Compounds Inhibiting Functions of TM4SF5 and Anti-cancer Composition Containing Chalcone Compounds	Jung Won Lee	China	20120523	ZL200780027477.7
18	Application	Fluorescent glucose analogue and usage thereof	Seung Bum Park	Rep. of Korea	20120522	1011509670000
19	Application	A novel antibody inhibiting osteoclastogenesis	Hyun Bo Shim	Rep. of Korea	20120521	1020120053868
20	Application	New compounds having a spiro chiral carbon, process for preparing the same and pharmaceutical composition comprising the same	Seung Bum Park	Rep. of Korea	20120518	1011498780000
21	Application	Composition comprising Δ5-2-oxopiperazine derivative for inducing differentiation of mesenchymal stem cells into chondrocytes	Seung Bum Park	Rep. of Korea	20120510	1020120049740
22	Application	Novel aniline derivatives and use thereof	Sunghoon Kim	Rep. of Korea	20120420	1020120041622
23	Application	Novel aminopyridine derivatives and use thereof	Sunghoon Kim	Rep. of Korea	20120420	1020120041623
24	Application	Device and Method of Generating In Vitro Blood Vessels	Noo Li Jeon	Rep. of Korea	20120418	1020120040613
25	Application	Device and method of generating in vitro blood vessels	Noo Li Jeon	China	20120418	201210120271.1
26	Application	Device and method of generating in vitro blood vessels	Noo Li Jeon	Europe	20120418	2526978
27	Application	Direct preparation of functional insulin producing cell from human dermal fibroblasts	Kyung Sun Kang	Rep. of Korea	20120413	1020120038781
28	Application	METHOD OF PREPARING HETERO-BIARYL PYRIDINE DERIVATIVE COMPOUNDS, AND HETERO-BIARYL PYRIDINE DERIVATIVE COMPOUNDS PREPARED THEREBY	Seung Bum Park	Rep. of Korea	20120330	1011341940000
29	Application	Method for Screening Anti-cancer Compounds Inhibiting Functions of TM4SF5 and Anti-cancer Composition Containing Chalcone Compounds	Jung Won Lee	Japan	20120224	4932005
30	Application	Crystal structure and peptide inhibitors of HAUSP deubiquitinase	Myung Hee Kim	PCT	20120222	PCT/US2012/026198
31	Application	Composition containing indole and indazole derivatives for inhibition of cancer metastasis	Sunghoon Kim	Rep. of Korea	20120127	1020120008503
32	Registration	method for screening an agent preventing or treating cancer using glycyl-tRNA synthetase and cadherin	Sunghoon Kim	Rep. of Korea	20111010	1020110103306
33	Registration	Aminoacyl-tRNA synthetases and tumorigenesis: More than housekeeping	Sunghoon Kim	U.S.A.	20110926	61/539221
34	Registration	Novel use of leucyl tRNA synthetase	Sunghoon Kim	Rep. of Korea	20110922	1020110095893
35	Registration	Novel anti-cancer composition	Sunghoon Kim	Rep. of Korea	20110804	1020110077863
36	Registration	Phenyl-(4-phenyl-thiazol-2-yl)-amine derivatives exhibiting regulation effect of Oct4, c-Myc and Sox2 in the stem cells and cancer cells	Kyung Sun Kang	U.S.A.	20110401	61/470884
37	Registration	CD49F PROMOTING PROLIFERATION, MULTIPOTENCY AND REPROGRAMMING OF ADULT STEM CELLS THROUGH PI3K/AKT/GSK3 PATHWAY	Kyung Sun Kang	PCT	20110218	PCT/KR2011/001103

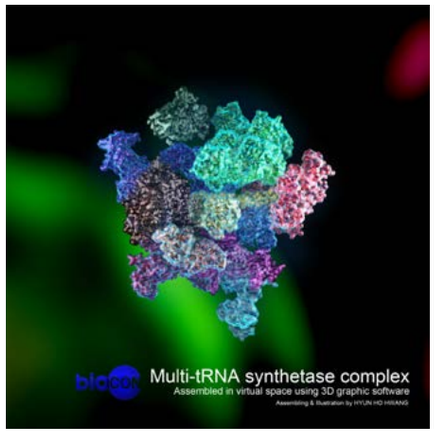
3. MOU

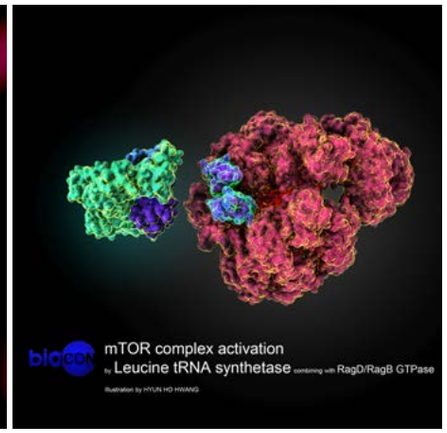
ISS

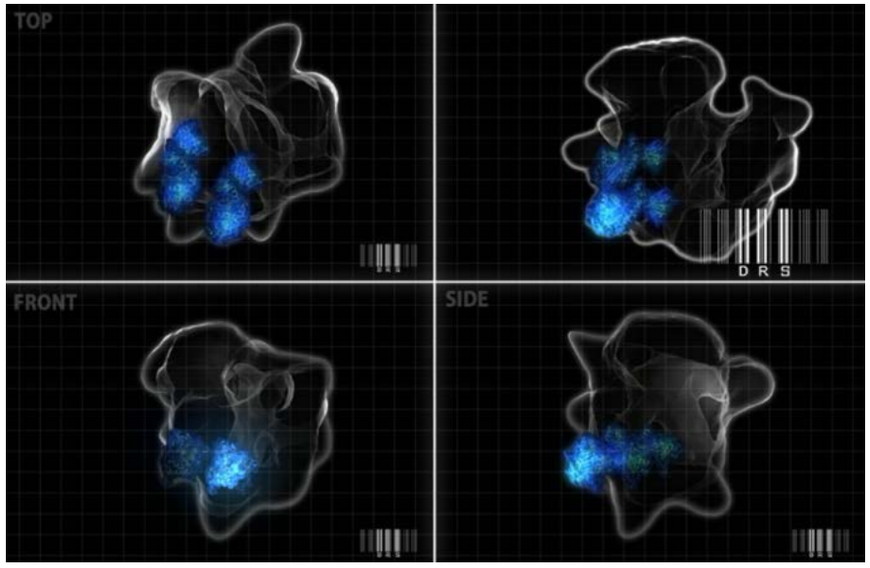
The Discovery Management Group

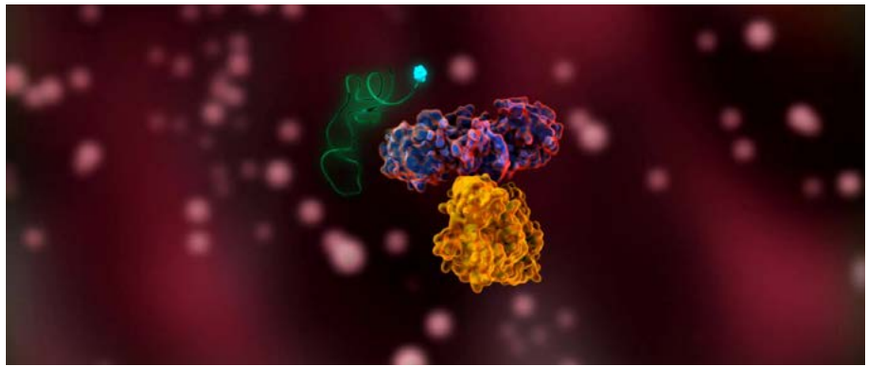
4. Cultural Activities

Biomedical Illustration









Cartoon

BMC Systems Biology

PharmDB

Rational drug repositioning guided by an integrated pharmacological network of protein, disease and drug.

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2

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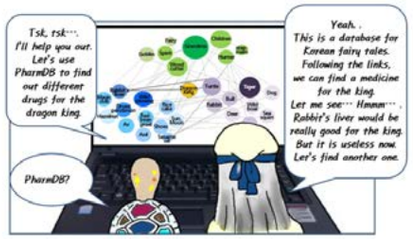
4



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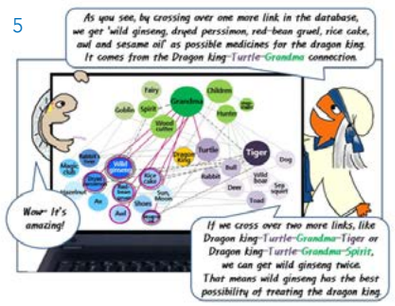

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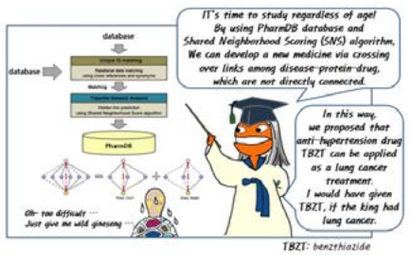


TBZT: benzthiazide

7

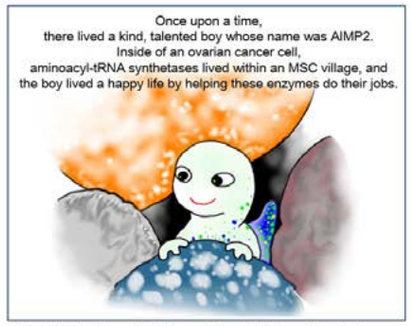
Thus, Turtle gave wild gingseng from Spirit Cello to the dragon king and the dragon king recovered his health completely. Believe it or not.

JMCB

DX2 as an effective target against chemoresistant ovarian cancer

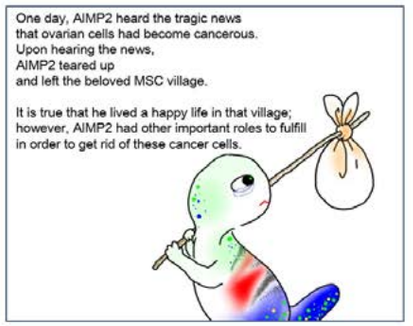
Splicing variant of AIMP2 as an effective target against chemoresistant ovarian cancer

1



Aminoacyl-tRNA synthetases (ARSs): They are in charge of cellular protein synthesis.
MSC: muti-tRNA synthetase complex consisting of 9 ARSs and 3 cofactors (AIMP1, 2, and 3).

2



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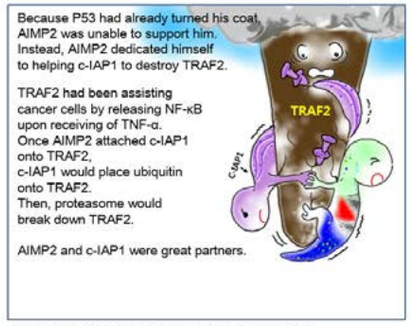
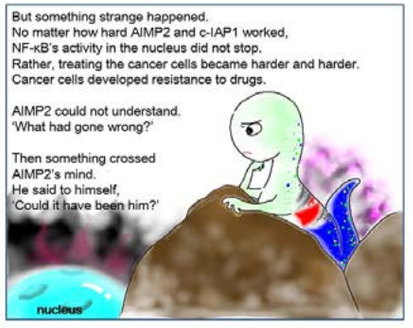


P53: A tumor suppressor. P53 mutations are observed in many cancers.
c-IAP1: E3 ubiquitin ligase. It induces proteosome-mediated TRAF2 degradation by polyubiquitination.
TRAF2: TNF-receptor associated factor 2. The key regulator of TNF-α signaling.
NF-κB: It enhances proliferation of drug-resistant cancer cells upon TNF-α signal.

4



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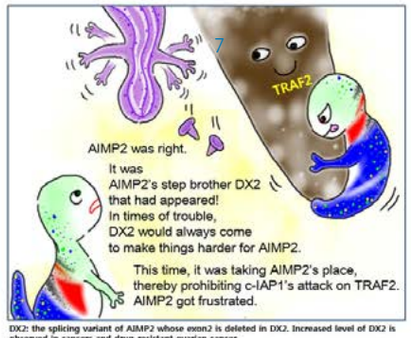
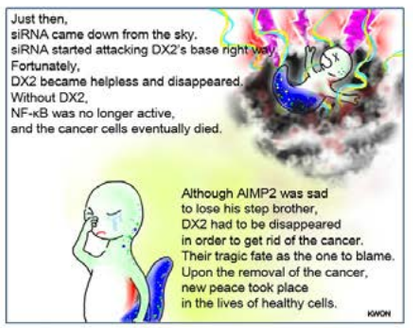


DX2: the splicing variant of AIMP2 whose exon2 is deleted in DX2. Increased level of DX2 is observed in cancers and drug-resistant ovarian cancer.

6



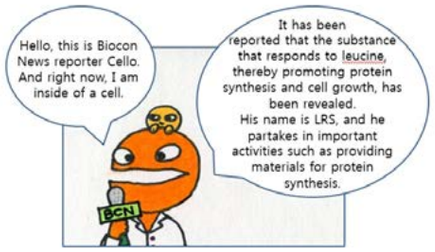
siRNA: It facilitates specific mRNA degradation by binding to the mRNA, resulting a reduction in the end-product protein level.

Cell

LRS as a Leucine Sensor

Leucyl-tRNA Synthetase Is an Intracellular Leucine Sensor for the mTORC1-Signaling Pathway

1



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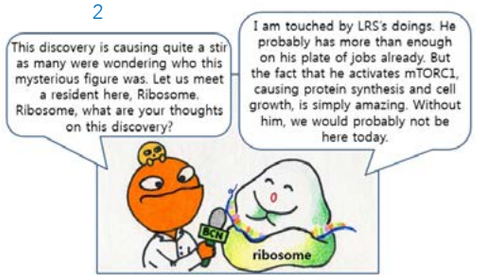

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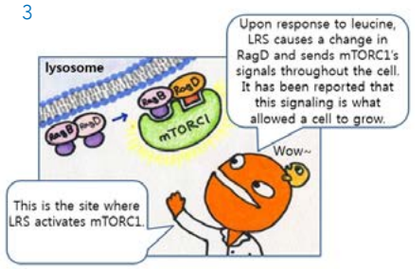

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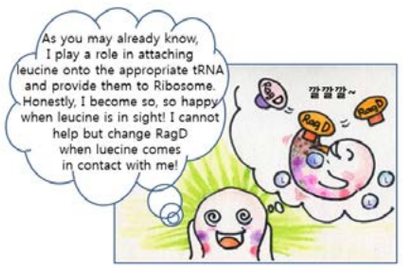

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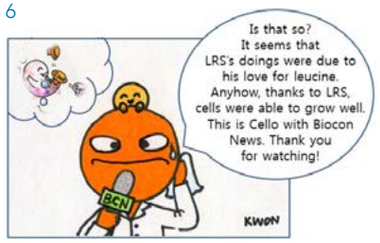
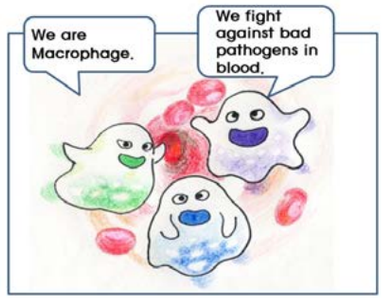


PNAS

What's GRS?

Secreted human glycyl-tRNA synthetase implicated in defense against ERK-activated tumorigenesis

1



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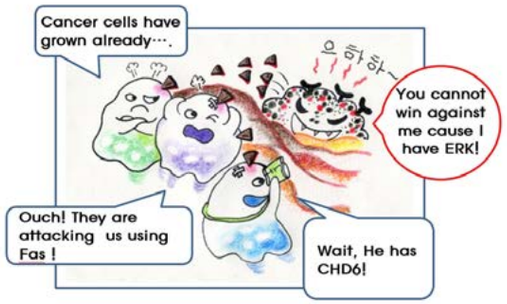

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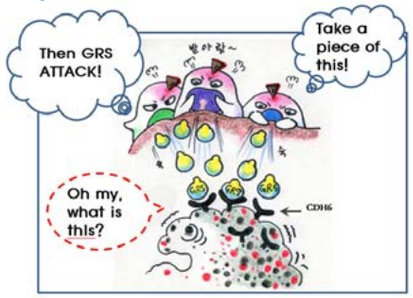

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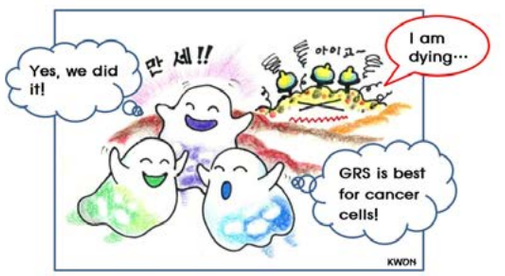
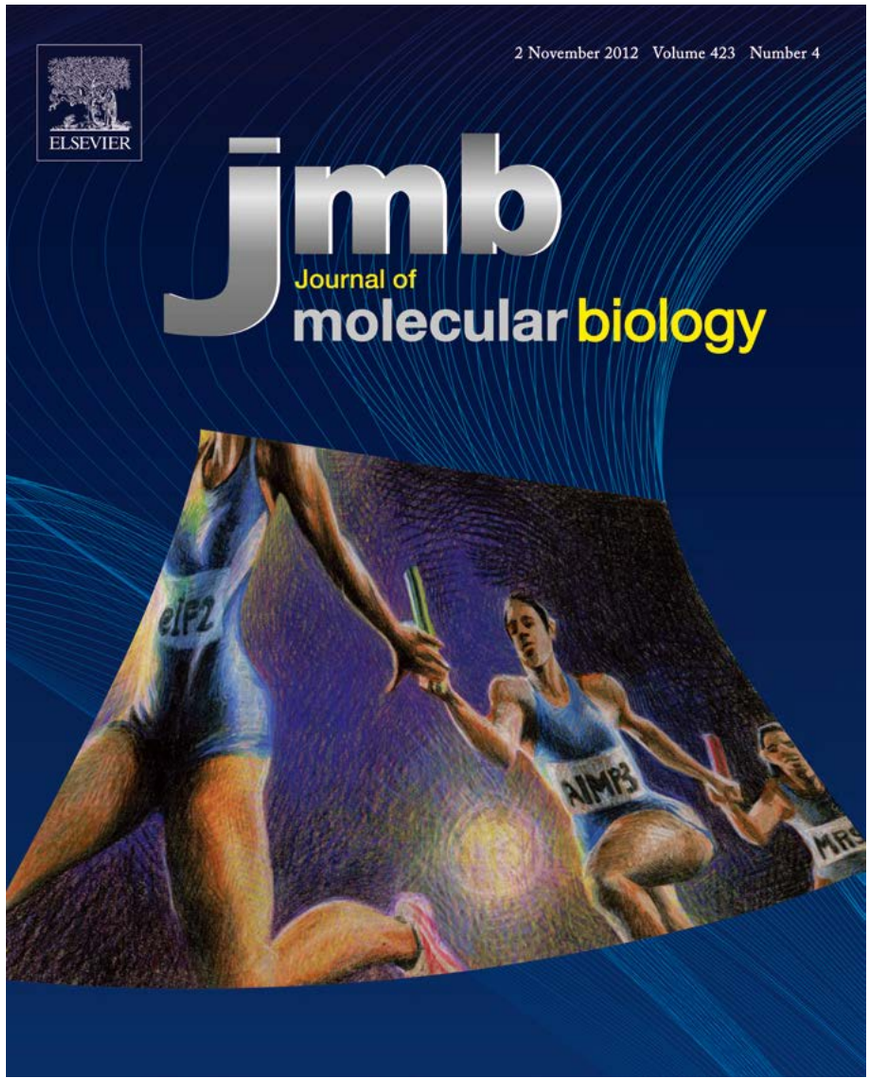


Cover Art

AIMP3/p18 is a factor bound to methionyl-tRNA synthetase (MRS) that charges methionine to the initiator tRNA. AIMP3/p18 takes over the methionine-charged initiator tRNA from the enzyme and passes it to initiation factor complex, eIF2. In this illustration, the role of AIMP3 in the delivery of initiator tRNA is symbolized as running a relay. See article by Kang et al. in this issue pp. 475–481. Artwork by Jean Kim.



Bio-Art Contest

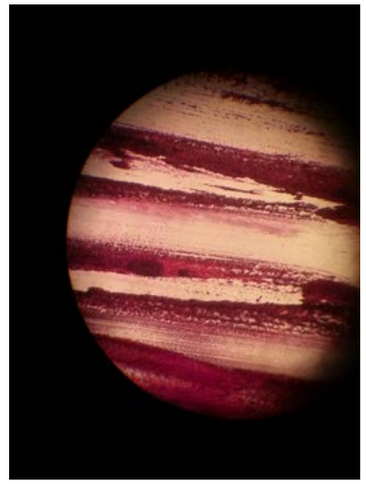
The first Bio-Art Contest organized by Biocon and Seoulin Co., Ltd. in Korea.

Bio-Art Contest Winners

Beauty of Nature

Life of Tree

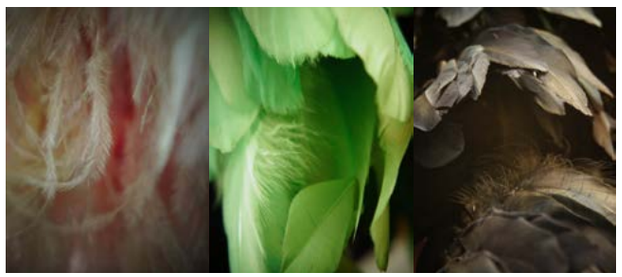
Nature and Human

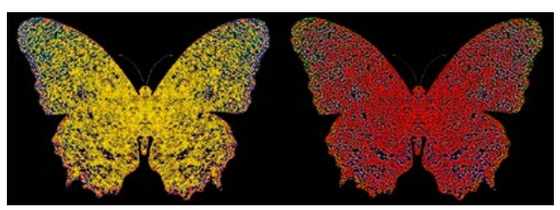


Jupiter

Plants Equipment


Link of Zooids


Transplant


Bless


Flying

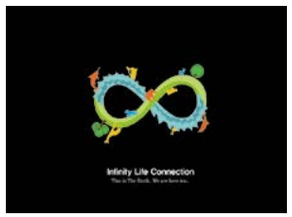

Nature and Human


Link of Life and Birth


Tree


Deja vu

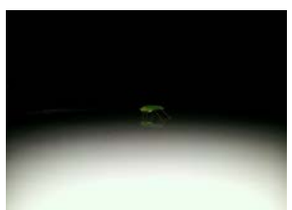

Origin

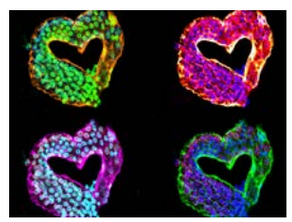


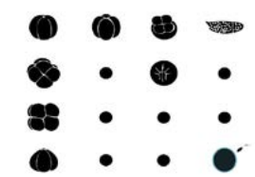
Infinity Life Connection

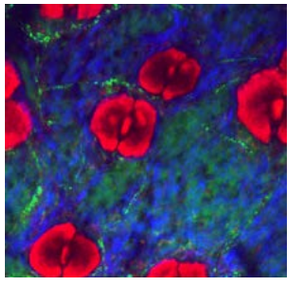
The Creation of Protein

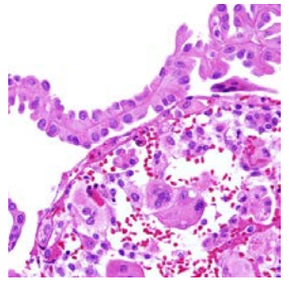

Two and Four


Life and Death


Heart of Life


Think, Dream


Flowers on Skin


Wisdom of Snake


Treatment of Life


Neural Networks from Life

5. Biocon People

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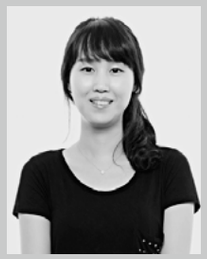

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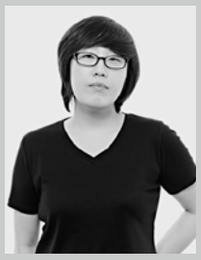

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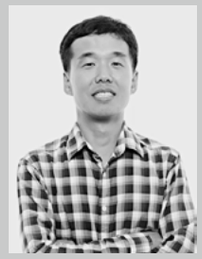

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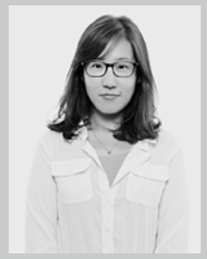

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제1회 의약바이오컨버전스연구단 Workshop
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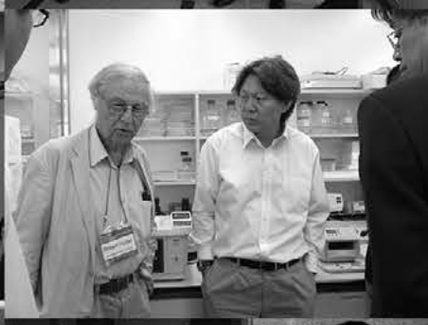
AICT

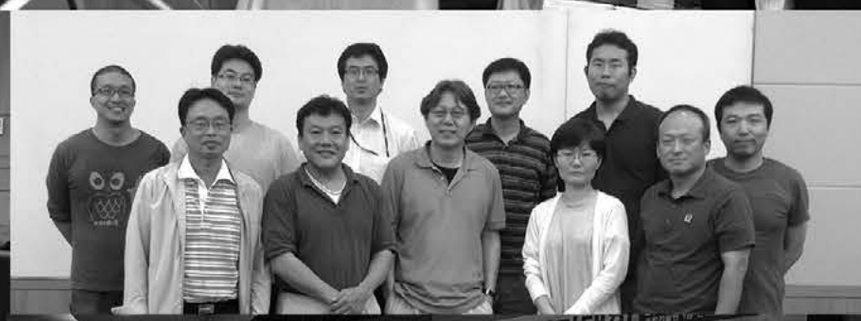


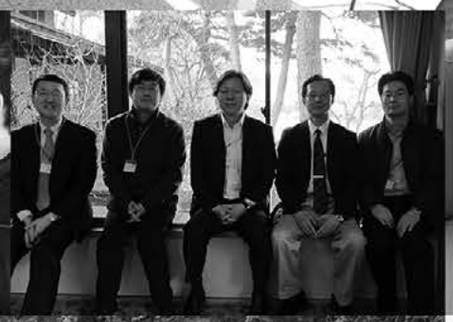












2nd PharmDB 경진대회