### Track 5(iii), 5(iv)

#### 5(iii): Hormone Replacement Therapy

#### 5(iv): Molecular-Targeted Therapies

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#### Session Introduction

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Title: Targeting the BCR-ABL tyrosine kinase in chronic Myeloid Leukemia as a model of rational drug design in cancer
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Title: Microtubule: A target for withaferin-a induced cell death
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Title: Molecular basis of anti-inflammatory strategies in cancer cachexia
Dr. Marilia Seelaender, University of Sao Paulo, Brazil

Title: Adenovirus Library for Novel Transductional Targeting
Dr. Yamamoto Masato, University of Minnesota, USA
Expression of the p53 target SERPINE1 (PAI-1) gene is required for human tumor cell migration upon plastic conversion to a stem cell-like phenotype in response to TGF-β1+EGF

Paul J. Higgins
Albany Medical College, USA

The emergence of highly aggressive, cancer stem cell-like, subtypes of human squamous cell carcinoma (SCC) reflects increased transforming growth factor-β1 (TGF-β1) synthesis and epidermal growth factor receptor (EGFR) amplification. Cooperative TGF-β1/EGFR signaling promotes cell migration and induces expression/activation of proteases (e.g., plasminogen, MMPs) and protease inhibitors that regulate stromal remodeling resulting in the acquisition of an invasive phenotype. Paradoxically, plasminogen activator inhibitor type-1 (SERPINE1,PAI-1), the major inhibitor of plasmin generation, is also upregulated under these conditions and is an early event in tumor progression. Increased PAI-1 expression temporally and spatially modulates plasmin-initiated pericellular proteolysis, preserving a stromal scaffold permissive that facilitates invasive potential. Combined TGF-β1+EGF treatment was used to investigate mechanisms underlying induced epithelial-to-mesenchymal transition (EMT) in ras-transformed human keratinocytes. Dual stimulation with TGF-β1+EGF resulted in keratinocyte "plasticity" and pronounced colony dispersal. Transcriptome analyses indicated that cells undergoing EMT expressed high β1 integrin levels and possessed stem cell-like characteristics. The most up-regulated transcript encoded PAI-1, an established marker of aggressive carcinoma cells and a functional promoter of cell migration suggesting that PAI-1 plays a critical role in epithelial stem cell biology. PAI-1 knockdown alone effectively inhibited TGF-β1+EGF-dependent cell scattering, indicating a functional role for this SERPIN in the dual-growth factor model of induced motility. Identification of signaling networks and their effect on specific invasion-promoting target genes, such as PAI-1, may lead to the development of pathway-specific therapeutics that impact late-stage events in human cutaneous epithelial tumor progression. Supported by grants from the NIH (GM57242) and the NYSDOH Empire State Stem Cell Trust Fund (C024312).

Biography
Dr. Paul J. Higgins received his Ph.D. in molecular biology from New York University. He was a post-doctoral fellow and Assistant Member at the Memorial Sloan-Kettering Cancer Center before assuming the Directorship of the Center for Cell Biology & Cancer Research at Albany Medical College. Dr. Higgins has published more than 250 papers, served on a number of NIH and international review panels and is an Editor of various biomedical journals. He was the recipient of the University of Florida College of Medicine Excellence Award in Molecular Medicine in 2008.
Molecular targets of cardiac hormones in cancers

David L. Vesely
James A. Haley Veterans Hospital/University of South Florida Health Sciences Cardiac Hormone Center, USA

One gene in the heart synthesizes four peptide hormones, i.e., long-acting natriuretic peptide, vessel dilator, kaliuretic peptide and atrial natriuretic peptide. These four peptides decrease up to 97% of human pancreatic, breast, colon, ovarian, kidney and prostate adenocarcinomas as well as glioblastomas of the brain, small-cell and squamous cell lung carcinoma cells in cell culture. When infused subcutaneously for 28 days with weekly fresh hormones at 3 nM min⁻¹ kg⁻¹ body weight in athymic mice, they eliminate up to 80% of the human pancreatic adenocarcinomas, 2/3rds of human breast adenocarcinomas, and up to 86% of human small-cell lung cancers with treated mice living a normal lifespan. These cancers never reoccur in the primary site in the lifespan of the mice. Their mechanisms(s) of action in cancer cells includes a 95% inhibition of Ras, 96% inhibition of ERK 1/2 kinases, and 98% inhibition of MEK 1/2 kinases. Mitogens such as epidermal growth factor which stimulate Ras and ERK 1/2 kinases have their effects completely blocked by these cardiac hormones. The cardiac hormones do inhibit ERK 1/2 kinases in healthy cells. In addition to inhibiting the Ras-MEK 1/2-ERK 1/2 kinase cascade, they enter the nucleus as shown by Immunocytochemical techniques where they inhibit DNA synthesis.

Biography

David L. Vesely, M.D., Ph.D., completed his M.D. and Ph.D. degrees simultaneously in 3 years at the University of Arizona Medical School and did his post-graduate training at the University of Miami Medical School. He is Chief of Endocrinology, Diabetes and Metabolism at the James A. Haley Medical Center and Professor of Medicine, Molecular Pharmacology and Physiology and Director of the Cardiac Hormone Center at the University of South Florida Medical School, Tampa, Florida, USA. He is the author of 315 peer-reviewed articles and 3 books. He received the 2007 Service to America Career Achievement Medal.
Beta-glucans as anticancer agents
Anshu Agrawal, Sudhanshu Agrawal and Sudhir Gupta
Department of Medicine, University of California-Irvine, USA

Pattern-recognition receptors (PRRs) detect molecular signatures of microbes and initiate immune responses to infection. Immune responses generated by prototypical PRRs such as Toll-like receptors (TLRs) have been widely investigated. In contrast, the immune responses initiated by other classes of putative PRRs remain ill defined. C-type lectins are a class of PRRs that recognize carbohydrate structures which are often part of microbial pathogens. Dectin-1 is a C-type lectin receptor present on dendritic cells that recognizes fungal β-glucans. Our investigations suggest that Dectin-1 is not just an antigen uptake receptor but also a modulator or initiator of adaptive immune responses. Human dendritic cells stimulated with Curdlan, Dectin-1 agonist prime CD4 Th17 responses via IL-23 production. Furthermore, these CD4 T cells induce differentiation of B cells to secrete IgG and IgA. More importantly; these dectin-1 stimulated dendritic cells promote the expansion and differentiation of granzyme B expressing cytotoxic T lymphocyte that display high cytolytic activity against target tumor cells in vitro. The capacity of Curdlan-stimulated human DCs to induce differentiation of these cells makes them attractive target for manipulations in clinic against cancer.

Biography
Anshu Agrawal completed Ph.D. from Central Drug Research Institute, Lucknow and subsequently worked as a Research Scientist in the division of immunology at ICGEB, India. She won a scholarship to work in France and after completing postdoctoral studies is now working as a faculty in the Department of Medicine, University of California, Irvine since last 6 years. She is the recipient of the New Scholar award in aging from the Ellison Medical Foundation. She has published more than 30 papers and serves as an editorial board member and reviewer for several journals. Her primary area of interest is dendritic cells, innate immunity and aging.
Mechanical blocking of cancer cell division by progerin

Olga Moiseeva
University of Montreal, Canada

The nuclear lamina is a fibrous structure underneath the inner nuclear membrane. One of the main components of lamina is the intermediate filament protein lamin A. Different lamin A mutations lead to development of a wide range of diseases, termed laminopathies. The most severe laminopathy is Hutchinson-Gilford progeria syndrome (progeria), which is characterized by premature aging, but not accompanied by an increase in cancer incidence. Progerin is a lamin A mutant with 50-aa deletion near the C-terminus. The inhibition of cancer cell proliferation by progerin is a consequence of accumulation of polymeric progerin formations in lamina that physically blocks mitosis.

Based on our results with progerin, we propose to use a mechanical approach in cancer therapy. Such an approach might work despite the mutations present in cancer cells, and therefore can be also effective at the late stages of cancer development. The disadvantage of the mechanical approach is that this approach could be toxic for normal dividing cells. To decrease the toxicity, targeted therapy can be used. Theoretically, this mechanical approach does not have to be limited to the nuclear lamina since different targets can be physically blocked inside and outside the cells. For example, a stable polymeric cage could be created around cancer cells to provide a physical barrier to proliferation that could act independently of any mutations. Any or several specific cancer receptors can be used, including those promoting proliferation. A wide range of polymeric nanoparticles is now available, magnetic nanoparticles can also be used.

Biography
Olga Moiseeva has completed her Ph.D from Pushchino State University and postdoctoral studies from University of Montreal.
The transcriptional landscape of nasopharyngeal carcinoma defined by RNA-seq

Mu-Sheng Zeng
State Key Laboratory in South China, Sun Yat-sen University Cancer Center, China

Next-generation sequencing technology is a powerful and cost-efficient tool for ultra-high-throughput transcriptome analysis. We applied paired-end RNA-seq to generate a deep unbiased transcriptome map of an EBV positive nasopharyngeal carcinoma (NPC) cell C666 and normal cell NPEC2. Using effective bioinformatics pipelines, we unambiguously detected many differentially expressed genes, novel transcripts, a variety of transcript isoforms and chimeric transcripts. Most importantly, we have identified a novel fusion gene which might play an oncogenic function in pathogenesis of NPC. Finally, we found that 78% EBV genes are transcribed, which indicate that the expression pattern of EBV in NPC is more complex than previously expected.

Biography

Dr. Zeng received his PhD degrees from Sun Yat-sen University of Medical Sciences and then worked as a postdoctoral fellow at the Department of Radiation Oncology in Tufts University-New England Medical Center in Boston. Currently, Dr. Zeng is a principal investigator in the State Key Laboratory in South China, China. He has published more than 30 papers in reputed journals.

Dr. Zeng’s research on EBV variation led to the analysis of the whole genomic sequence from a Cantonese NPC derived EBV. The studies on cellular oncogenes led to identification of the potential role of the polycomb protein Bmi-1 in NPC as well as establishment of Bmi-1 immortalized nasopharyngeal epithelial cell lines. His current research focuses on the molecular events required for early transformation of nasopharyngeal epithelial cells as well as early diagnosis of NPC.
Nanoformulated nanocarriers with modified lactoferrin for cancer and bio-distribution through MRI

Jagat R. Kanwar, Rupinder Kanwar and Ganesh Mahidhara
Institute for Technology and Research Innovation (ITRI), Deakin University, Australia

Background: At nano scale, the fundamental and vital properties of matter can be changed, which can be used for daunting task such as oral administration of bio-macromolecules to be able to achieve sustained delivery, controlled release, target specific delivery and combinatorial therapy.

Objectives: Main objective of the study was to develop, characterize and see the bio-distribution of iron saturated lactoferrin protein loaded novel ceramic nanocarriers to deliver orally and monitor these tumours MRI imaging in xenograft colon cancer.

Methods and Results: In our study, we demonstrate the formulation of a novel alginate enclosed, chitosan coated ceramic anti cancer nano carriers (ACSC NC). These NC were loaded with multi-functional anti cancer bovine lactoferrin (bLf), a natural milk based protein, for improvement of intestinal absorption, in order to develop a novel platform to carry anti cancer protein and/or peptides for oral therapy. Size, morphology, internalization and release profiles of the ACSC NC under varying pH were determined. Furthermore, uptake of these NC in vitro in colon cancer cell lines was analyzed, by measuring the endocytosis and transcytosis. NCs were characterised through various physical and biological assays. Transcytosis studies indicate the transcytosis of the NC, with minimal damage to the Caco-2 cell monolayer. In conclusion, these NC can be used for future targeted protein/peptide or nucleic acid based drug delivery to treat fiddly diseases such as cancer and neurodegenerative disorders. Lf+ loaded ACSC NC significantly reduced tumour vascularity and blood flow, and increased anti-tumour cytotoxicity, tumour apoptosis and the infiltration of tumours by leukocytes. Lf+ increased the average weight of the spleens of tumourbearing mice by ~20%, accompanied by a major increase in the numbers of particular leukocyte subsets in the spleen. CD4+, CD8+, NK, IFN-γ+-expressing and dendritic cell numbers in the spleen were significantly (P<0.001) increased compared to corresponding cell numbers for mice maintained on the control diet. Lf+ bound to the intestinal epithelium and was preferentially taken up within Peyer’s patches. It increased the production of Th1 and Th2 cytokines within the intestine and tumour, including TNF, IFN-γ, as well as nitric oxide that have been reported to sensitize tumours to doxorubicin chemotherapy. Importantly, it restored both red and white peripheral blood cell numbers depleted by doxorubicin chemotherapy, potentially fortifying the mice against cancer. In summary, bLf is a potent natural adjuvant and fortifying agent for augmenting cancer chemotherapy, but needs to be saturated with iron and administered orally in Lf+ loaded ACSC NC to be effective. Bio-distribution of iron saturated lactoferrin was determined my MRI and confirmed by other imaging techniques. We also compared our results with the doxorubicin and taxol loaded ACNC-NPs.

Conclusion: Taken together, our results are highly encouraging for the development of combination nano-therapeutic strategies that combine gene silencing and drug delivery to provide more potent and targeted therapeutic, especially in late and metastatic breast cancer.

Biography
Dr Kanwar is an immunologist and molecular biochemist with an international reputation in investigating fundamental and applied molecular aspects of cancer and chronic inflammation. He did his PhD from Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. Before joining Deakin University in 2006, he was a Senior Scientist/Senior Research Fellow in the University of Auckland, Auckland, New Zealand. During the past decade his research both academic and commercial has centered on understanding the pathophysiological mechanisms and/or finding treatments for a variety of chronic inflammatory diseases and different types of cancer. Dr Kanwar has published 55 research articles, 12 invited reviews and 5 book chapters, in highly ranked, international, peer-reviewed journals. These publications have added to the body of knowledge in the fields of immunology, cancer gene therapy, nanomedicine, cell biology and biotechnology, and have extended these disciplines. He is a key inventor on 9 international patents and has provided consultancy to 5 Biotechnology based companies. He is a member of editorial board for 7 international journals and a nominated member of more than 12 national and international societies including American Society of Nanomedicine. He has extensive and close collaborations with colleagues from New Zealand, Australia, Singapore, India, China and USA.
Alternative splicing of Kruppel-like factor 4 plays a role in colorectal tumorigenesis

Seung J. Baek and Jae Hoon Bahn
University of Tennessee College of Veterinary Medicine, USA

Most human genes undergo alternative splicing, and many abnormal splicing processes are associated with human diseases. However, the molecular relationship between alternative splicing and tumorigenesis is not well understood. Here, we found novel Krüppel-like factor 4 (KLF4) splicing variants produced by exon skipping in human cancer cell lines as well as colon tumor tissues. To elucidate mechanism of the KLF4 alternative splicing, we developed KLF4 minigene system and found that RNA binding motif protein 5 (RBM5) plays an important role in KLF4 splicing, as assessed by gain and loss of functional studies. Several anti-tumorigenic compounds were also tested for the KLF4 splicing. Interestingly, sulindac sulfide restored wild type KLF4 (KLF4\textsuperscript{L}) expression and this is mediated by dephosphorylation of RBM5. Another splicing variant, small KLF4 (KLF4\textsuperscript{S}), localizes in the cytoplasm and nucleus, and antagonizes transcriptional activity of wild type KLF4. Our data suggest that RBM5 plays a pivotal role in the alternative splicing of KLF4, and these splicing variant forms may impact tumorigenesis.

Biography
Dr. Seung Baek completed his Ph.D from University of Maryland School of Medicine and postdoctoral studies from NIEHS/NIH. He is the director of Lab of Environmental Carcinogenesis. He has published more than 85 papers in reputed journals and serving as an editorial board member of several journals.
Inhibition of adenoid cystic carcinoma cell growth and metastasis by knockdown of ADAM 10 expression via RNA interference

Zhiyuan Zhang, Qin Xu, Xiuming Liu and Wantao Chen
Ninth People’s Hospital, Shanghai Jiao Tong University School of Medicine, China

Background: Adenoid cystic carcinoma is one of the most common types of salivary gland cancers. The poor long-term prognosis for patients with adenoid cystic carcinoma is mainly due to local recurrence and distant metastasis. Disintegrin and metalloprotease 10 (ADAM 10) is a transmembrane protein associated with metastasis in a number of diverse of cancers. The aim of this study was to analyze the relationship between ADAM 10 and the invasive and metastatic potentials as well as the proliferation capability of adenoid cystic carcinoma cells in vitro and in vivo.

Methods: Immunohistochemistry and Western blot analysis were applied to detect ADAM 10 expression levels in metastatic cancer tissues, corresponding primary adenoid cystic carcinoma tissues, adenoid cystic carcinoma cell lines with high metastatic potential, and adenoid cystic carcinoma cell lines with low metastatic potential. RNA interference was used to knockdown ADAM 10 expression in adenoid cystic carcinoma cell lines with high metastatic potential. Furthermore, the invasive and metastatic potentials as well as the proliferation capability of the treated cells were observed in vitro and in vivo.

Results: It was observed that ADAM 10 was expressed at a significantly higher level in metastatic cancer tissues and in adenoid cystic carcinoma cell lines with high metastatic potential than in corresponding primary adenoid cystic carcinomas and adenoid cystic carcinoma cell lines with low metastatic potential. Additionally, silencing of ADAM 10 resulted in inhibition of cell growth and invasion in vitro as well as inhibition of cancer metastasis in an experimental murine model of lung metastases in vivo.

Conclusions: These studies suggested that ADAM 10 plays an important role in regulating proliferation and metastasis of adenoid cystic carcinoma cells. ADAM 10 is potentially an important therapeutic target for the prevention of tumor metastases in adenoid cystic carcinoma.
Peptide-Targeted Chemotherapy against Breast Cancer

Chin-Tarng Lin
National Taiwan University, College of Medicine, Taiwan

To obtain a better efficacy of chemotherapy we used one nasopharyngeal carcinoma (NPC) line to select a 12-mer specific peptide which can bind specifically to the surface of NPC cells from a phage-displayed random peptide library. This peptide has met several criteria for targeted drug delivery into the NPC solid tumor. In vitro the peptide can bind specifically to the cell surfaces of most NPC cell lines and biopsy specimens; the peptide-linked liposome containing fluorescent substance is capable of binding to and translocation across cell membranes; in vivo, this specific peptide can bind and accumulate in the NPC xenograft in SCID mice, but not in normal organs; similarly, the peptide-linked liposome carried doxorubicin (Dox) not only can cause marked cytotoxicity of NPC cells in vitro, it can also suppress markedly the xenograft growth in SCID mice without systemic side effect. In addition, FITC-labeled L-peptide could also bind to breast cancer cells by FACScan. In MDA-231 breast cancer xenografts, L-peptide-labeled Dox could inhibit not only the in situ xenograft but also the metastatic tumor nodules with minimal adverse effect. The L-peptide linked iron oxide (Fe3O4) nanoparticles could be localized in MDA-231 cultured cells and on the breast cancer surgical specimens. In conclusion, the novel peptide we identified can be used for targeted chemotherapy with high efficacy and without systemic side effect. Apparently, the peptide-targeted chemotherapy is superior then the conventional chemotherapy, and application of this peptide-targeted therapy against breast cancer may let this cancer becomes a controllable disease.

Biography

Dr. Chin-Tarng Lin was awarded his D.D.S. degree from National Taiwan University (NTU), Taipei, Taiwan in 1963 and obtained his Ph. D. degree in 1975 from the Graduate Institute of Texas Medical Branch at Galveston, Texas, U.S.A. He was a Professor in the Institute and Department of Pathology, NTU since 1987 and became an Emeritus Professor in 2009. He has established 10 nasopharyngeal carcinoma (NPC) cell lines, and developed the peptide-targeted chemotherapy method against cancers. He has published more than 87 papers in reputed journals. The published data strongly indicate that peptide-targeted chemotherapy has a great potential for cancer treatment.
Targeting the BCR-ABL Tyrosine Kinase in Chronic Myeloid Leukemia as a model of rational drug design in cancer

Zámečníkova Adriana
Kuwait Cancer Control Center, Department of Hematology, Kuwait

Many biological and clinical features of chronic myeloid leukemia make it a paradigm of rational drug design in human cancer. Chronic myeloid leukemia was the first malignancy to be linked to a clear genetic anomaly, the Philadelphia chromosome and at present, it is probably the best understood of all human malignancies. Studies of the disease pathology revealed, that the molecular consequence of the Philadelphia translocation is a novel fusion gene, BCR-ABL, which encodes a constitutively active tyrosine kinase with wholesale range of biological activities. Animal models have validated the direct role of the BCR-ABL protein in malignant transformation and subsequent research confirmed that the enhanced tyrosine kinase activity of BCR-ABL is essential and sufficient for the leukemogenesis. The very existence of a single genetic abnormality, presented in essentially all patients made it a potential target for molecularly designed therapeutic approaches for the disease. The advent of tyrosine kinase inhibitors, designed specifically to inhibit the tyrosine kinase activity of the BCR-ABL protein represents one of the major innovations in cancer therapy and may serve as a pattern how discoveries of disease pathogenesis may be translated into the development of successful targeted therapies in cancer medicine.

Biography
Dr. Zámečníkova Adriana, PhD has a Masters degree from Clinical Genetics and has completed her Ph.D from Comenius University, Slovakia in 2001. Registered by Health Professions Council, UK, London, as a Clinical Scientist and by Health Practitioners Competence Assurance, New Zealand, as a Medical laboratory Scientist. From 1997 she was appointed as a Head of the Department of Cancer Genetics at National Cancer Institute, Slovakia and from 2001 she is working as a supervisor of Cancer Genetics Laboratory at Kuwait Cancer Control Center, Kuwait. She has published more than 40 papers in reputed journals and participated as a speaker in various meetings and conferences.
Microtubule: A target for withaferin-a induced cell death

Sumita Sengupta1, Kamalini Ghosh1, Amlan Das2, Ansuman Lahiri1 and Gopal Chakrabarti2

1Department of Biophysics, University of Calcutta, India
2Department of Biotechnology University of Calcutta, India

Background: Withaferin-A effectively induces cell cycle arrest and apoptosis by targeting multiple proteins in variety of carcinomas. WA limits migratory and invasive capabilities of cancer cells by interfering with actin cytoskeleton and intermediate filament protein vimentin, but, heretofore, no evidence has been reported whether it can binds to tubulin directly resulting in inhibiting microtubule assembly.

Methods: MTT assay was done to get the IC-50 value of WA for cancer cells, cell cycle arrest was determined by FACS, apoptosis was found by AnnexinV/ PI staining, immune-cytochemistry was performed to check microtubular network within cells, cellular migratory activity was monitored by wound healing assay. In vitro tubulin polymerization was studied by light scattering technique, kinetics of WA-tubulin interaction was monitored by fluorometric assays and probable WA-tubulin interaction site was proposed by molecular modeling method.

Results: WA inhibited proliferation of cancer cells, caused S and G2-M arrest as well as apoptosis, caused significant disruption of interphase and spindle microtubules, inhibited microtubule polymerization of purified tubulin in vitro. Direct binding of WA to tubulin altered fluorescence of tubulin tryptophan residues, ANS-tubulin complex. Competition assays showed no binding of WA to colchicine binding site of tubulin. Molecular docking simulations indicated preferential binding site of WA to tubulin which is different from colchicine or vinblastin binding sites.

Conclusion: These findings provide strong evidence that WA suppresses microtubule dynamics within cells by directly binding to tubulin, thereby perturbs cancer progression.
Molecular basis of anti-inflammatory strategies in cancer cachexia

Marilia Seelaender
University of Sao Paulo, Brazil

Cancer cachexia is a paraneoplastic syndrome affecting the large majority of terminally ill cancer patients and is clinically characterized by a number of symptoms which are not overcome by standard nutritional supplementation or by pharmacological therapy. L-Carnitine has been tested in preliminary studies in human cachexia, resulting in improved fatigue and quality of life. Our results show that in experimental cachexia the marked alterations of lipid metabolism are suppressed by L-carnitine supplementation, and associated with increased survival. The anti-inflammatory effects of L-carnitine supplementation seem to be similar to those elicited by chronic physical exercise in cachectic animals and patients. We have shown that the expression of lipid metabolism-related proteins is restored to normal levels in the liver and muscle after exercise training, re-establishing cellular function. These results are associated with decreased local and systemic inflammation, to which the white adipose tissue markedly contributes in cachexia. The molecular basis of the effects of L-carnitine supplementation and of exercise training upon cancer cachexia, with special focus on the relevance of white adipose tissue, will be examined.
Adenovirus Library for Novel Transductional Targeting

Yamamoto Masato
University of Minnesota, USA

Adenovirus (Ad) vector and oncolytic adenovirus has been engineered as therapeutics taking advantage of high in vivo transduction efficiency. However, targeting by selective infection (transductional targeting) and its incorporation to virus-coding sequence has been a nightmare in many vectors including Ad vectors. A lot of targeting peptide-coding sequences have been placed into capsid coding regions but extremely limited number of the targeting moiety successfully worked in Ad capsid, presumably due to structural limitation of the virus structure. Thus, it is natural to screen the peptide presented on adenovirus capsid format from the beginning. However, to date, the library size achievable in Ad system has been low. Conventional system makes few plaques from 1ug viral DNA. The most advanced system with Cre-loxP system yields 10^6 order diversity. Recently, we have developed a novel hyper-efficient Ad vector generation system by overcoming three major bottle necks for Ad vector production by performing the process in fiber complementing producer cell with newly designed shuttle plasmid and rescue virus. We applied this technology for Ad targeting ligand library generation and achieved 10^10 diversity. High throughput screening of the library identified novel targeting motifs which selectively bind to cell surface protein highly expressed in several major cancers including pancreatic cancer. The oncolytic virus with one of these targeting motifs showed selective and potent antitumor effect in vitro and in vivo in the receptor positive cells. In summary, we have developed a new way to identify the adenovirus transductional targeting ligand. Such vectors with preferential distribution and the system to generate them are expected to be beneficial for the development of systemically injectable cancer targeted vector system.

Biography

Dr. Yamamoto, Masato obtained his M.D & Ph.D from Osaka University School of Medicine, Osaka, Japan. He is board-certified gastroenterologist in Japan. He has been working for cancer gene therapy with adenovirus vectors. His lab has developed a series of replication competent adenovirus vectors and is considered to be one of the leading labs for replication competent adenovirus vectors. His group has been a leading lab for the application of oncolytic virus in the field of GI cancers including pancreatic and esophageal cancers. He has rich experience of experiments with clinical materials and evaluation of the oncolytic viruses. He was awarded John R. Durant Award for Excellence in Cancer research 2001-Junior Faculty Category University of Alabama at Birmingham Comprehensive Cancer Center. The MCMRC Excellence Award at the 14th Intl. Conference on Gene Therapy of Cancer in 2005.