がんや難治性疾患の治療と診断に向けた抗体開発

浜窪　隆雄

膜タンパク質のバキュロウイルス上への発現系を用いて、がん細胞膜に高発現のマーカータンパク質に対するモノクローナル抗体を作製し、治療や診断に用いる方法を開発している。親和性の高い抗体と低ノイズ磁気ビーズを用いることにより、プロテオミクスによるタンパク質複合体の高感度解析系を構築した。より親和性が高くまた高機能を備えた抗体分子を設計する試みを開始し、目的に応じたバイオプローブの開発を目指す。

Profile

1982年京都大学医学部卒業。内科研修医・博士課程（細胞内プロテアーゼの研究；村地孝教授）を経て1987年より京大病院臨床検査部助手。1988年よりバンダービルト大学医学部生化学教室研究員（実験高血圧症の研究；稲上正教授）。1996年より東京大学先端科学技術研究センター分子生物医学部門助手（コレステロール代謝の研究；児玉龍彦教授）、2002年より同教授。モノクローナル抗体による治療薬・診断薬の開発。

ーFIRSTプログラム　田中プロジェクト　公開セミナー運営事務局ー

Funding Program for World-Leading Innovative R&D on Science and Technology(FIRST Program)
Development of the next generation mass spectrometry system, and contribution toward drug discovery and diagnostics

最先端研究開発支援プログラム（FIRST）

田中プロジェクト　日米がん研究公開セミナー

本プロジェクトは、世界最高性能の質量分析システムを開発し、
このシステムを用いたがんやアルツハイマー病の新たな診断・治療手法の確立に向けて、
バイオマーカーの発見やがん創薬のための標的分子候補の発見に繋げる研究開発を
進めています。本セミナーでは、プロジェクトの研究概要をご紹介すると共に、
国内外の著名な講師をお招きして、日米におけるがん研究の”今”をご紹介いたします。

■日　時／2011年10月26日（水）14:00より（開場13:30）
■会　場／㈱島津製作所 本社・三条工場内 研修センター4F

PROGRAM

14:00～14:20	田中耕一・島津製作所　田中最先端研究所 開会の挨拶　／　最先端プログラムについて
14:20～14:50	Prof. Matthew Meyerson Dana-Farber Cancer Institute
14:50～15:20	Prof. Matthew James Ellis (Washington University)
15:20～15:50	Prof. Raju Kucherlapati (Harvard University)
15:50～16:00	休憩
16:00～16:30	浜窪隆雄 教授 東京大学 先端科学技術研究センター
16:30～16:40	閉会の挨拶

Genomic analysis of human lung cancers

Matthew Meyerson

Cancer is a disease of the genome. High-throughput genome analysis tools now enable the detection of somatic alterations in cancer cells including point mutations, copy number alterations, translocations, and infections. Our approaches include next-generation sequencing of cancer genomes, exomes, and transcriptomes as well as single nucleotide polymorphisms (SNP) array analysis of copy number.

As part of "The Cancer Genome Atlas" or TCGA project of the National Institutes of Health, which aims to characterize the genomes of 10,000 human cancers, we are performing genomic analysis of lung carcinomas. In this presentation, I will discuss analysis of the genomes of squamous cell lung carcinomas. New results regarding mutations, genomic structure, and classification will be presented.

Profile

Matthew Meyerson is a leader in the field of cancer genomics with a focus on lung cancer. He serves as Professor of Pathology at Dana-Farber Cancer Institute and Harvard Medical School, and a Senior Associate Member of the Broad Institute. Together with Drs. Sellers, Johnson and Janne, the Meyerson group identified somatic mutations in the epidermal growth factor gene, EGFR, in lung adenocarcinomas, that predict response to EGFR kinase inhibitors. The laboratory has pioneered methods for cancer genome research, including copy number determination with single nucleotide polymorphism (SNP) arrays, leading to identification of oncogenes including NKX2-1, SOX2, and MCL1. In addition, the Meyerson group developed the computational subtraction approach to discovery of novel disease-causing microbes. For "The Cancer Genome Atlas" (TCGA), Dr. Meyerson is principal investigator of the Genome Characterization Center at the Broad Institute.
Dr. Meyerson received his M.D. from Harvard Medical School and his Ph.D. from Harvard University. He was a resident in Clinical Pathology at Massachusetts General Hospital and a post-doctoral fellow at the Whitehead Institute with Dr. Robert Weinberg. Dr. Meyerson was awarded the Paul Marks Prize in Cancer Research of Memorial Sloan-Kettering Cancer Center and the Team Science Award of the American Association for Cancer Research.

Patient-derived tumor explants for the development of proteogenomic maps of breast cancer.

Matthew J. Ellis

An unbiased approach to the generation unbiased whole cancer proteome maps to match the context provided by whole genome sequenced tumors, is likely to provide profound biological insights into cancer biology and generate clinically useful biomarkers and therapeutic target assessments. With support from a newly funded phase of the Clinical Proteomics Technology Assessment Centers (CPTAC) NCI program we are addressing the technical, bioinformatics and specimen accrual procedures to achieve this goal.

One of the early approaches we plan to take is take advantage of a breast cancer xenografting program at Washington University in St Louis we have dubbed Human and Mouse Linked Evaluation of Tumors (HAMLET). The goal of this program is to define the whole genome structure of a tumor growing in a patient, and compare it to the genome of tumor explants derived from that tumor growing as a xenograft in an immunodeficient mouse. Massively parallel sequencing allows us to be sure the mutations that are in the mouse xenograft were present in the progenitor human tumor and that they are somatic in nature because the patients whole genome was also sequenced. An example of this approach can be in a recent publication (Ding, Ellis et al Nature 2010, 464: 999-1005). We have now analyzed 16 additional tumors and we plan to use these models to address a number of biological and pharmacological questions.

One of the advantages of the HAMLET system is tumors can be accrued in a relatively pure form (sequence mapping suggests only 10% of the DNA in the tumors is of mouse origin) and samples can be snap frozen in relatively large amounts for proteomics. We have begun to analyze samples using sensitive proteomic technologies and preliminary data will be presented regarding our ability to detect proteins encoded by mRNAs arising from genes considered intrinsic to breast cancer, i.e. those with sufficient differential expression to be useful for disease categorization. We are also beginning to take advantage of our knowledge of the exact SNP structure of both the germ-line and somatic variations in the samples we are mapping to achieve accurate proteogenomic mapping experiments. Previously proteogenomic maps have used the reference genome. However this means that peptides that arise from variant DNA sequence, either inherited or somatically mutant, will not map accurately. By "recoding" the reference genome with the individual genomic information this problem is overcome. Currently we are mapping regions of gene amplification to try and identify the most abundantly over-expressed proteins in these regions, both because this may allow us to discern genetic drivers, and because it may allow us to identify biomarkers that may have clinical utility.

Profile

Professor of Medicine, Anheuser Busch Endowed Chair of Medical Oncology:
Head Section of Breast Oncology, Deptof Medicine, Washington UniversitySchool of Medicine,

Genetics and Genomics of Colorectal Cancer

Raju Kucherlapati

To understand the molecular changes in the initiation and progression of colorectal cancer the Cancer Genome Atlas (TCGA) network, examined a set of 224 tumor/normal pairs for changes in somatic copy number, chromosomal structural aberrations, expression profiling, promoter DNA methylation, miRNA expression and somatic mutations in all 23,000 genes. Our integrative analyses show that besides the well known genes such as APC, KRAS, PIK3CA and TP53 and pathways such as WNT, MAP Kinase, PI3 Kinase and TGFB there are several additional features that are important for tumor development. Low pass whole genome sequencing revealed several recurrent chromosomal translocations. Copy number analysis revealed focal amplifications and deletions in several genes including amplification of IGF2. DNA promoter methylation analysis revealed that a subset of samples have high levels of CIMP. Micro RNA analysis revealed that the abundance of number of miRNAs is altered in the CRC samples. Sequencing of all of the nearly 23,000 genes in each sample revealed many genes that are frequently mutated. We find alterations in many of the genes that have been implicated in CRC and other genes whose role in CRC has been under appreciated. Integrative analysis of the data enabled us to identify several critical pathways that are altered in specific subsets of the tumors. These observations suggest that it may be possible to develop novel therapeutic strategies for CRC patients based on the genetic/genomic profiles of their tumors.

Profile

Dr. Raju Kucherlapati, Ph.D. is the Paul C.Cabot Professor in the Harvard Medical School Department of Genetics. He is also a professor in the Department of Medicine at Brigham and Women's Hospital. Dr. Kucherlapati was the first Scientific Director of the Harvard Medical School-Partners Healthcare Center for Genetics and Genomics. His research focuses on gene mapping, gene modification, and cloning disease genes. He has chaired numerous NIH committees and served on the National Advisory Council for Human Genome Research and the NCI Mouse Models for Human Cancer Consortium. He is also a member of the Cancer Genome Atlas project of the National Institutes of Health. He is a member of the Institute of Medicine of the National academy of sciences and a fellow of the American Association for the Advancement of Science. He is a member of Presidential Commission for the Study of Bioethical Issues. Dr. Kucherlapati received his B.S. and M.S. in Biology from universities in India, and he received his Ph.D. from the University of Illinois at Urbana, as well as conducting post-doctoral work at Yale University.