NOBEL LAUREATE SESSION

BIOETHICS AND COVID-19; IT IS NOT ONLY THE VIRUS, THE DISEASE AND THE VACCINE

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Many bioethical questions have emerged in the rush to develop a vaccine for Covid-19 and care for the multitude of patients. These questions require careful attention in preparation for the next pandemic that will certainly come. Among the question are: i) How to prioritize treatment for those in need of respiratory assistance? ii) Can we prioritize the pandemic neglecting important issues such as climate change or campaigns to defeat infectious diseases in Africa, e.g., tuberculosis and malaria? iii) How to handle vaccine hesitancy and its sources? iv) What to do with "infodemics", the pandemics of disinformation and the huge damage they produce? (v) How to confront the rise of racism? Some problems are related to bioethical issues we confront while ushering in the era of personalized medicine. Among the issues that will certainly need redefinition are the pillars of 'canonical' medicine: the patient, the disease, and the treatment.

ARCHAIC GENOMICS

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Our laboratory has generated high-quality genome sequences from Neandertals and Denisovans, archaic hominins who shared a common ancestor with present-day humans about half a million years ago. Analyses of these genomes show that gene flow occurred among modern human ancestors and archaic hominins. As a consequence, archaic genetic variants occur in present-day people. I will discuss the effects of some of these variants as well as of some variants that appeared and rose to high frequencies in modern humans since their divergence from the archaic hominins.

THE MANY ROLES OF DNA METHYLATION IN BACTERIA

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There are three kinds of DNA methylation in bacteria – N6-methyladenine, N4-methylcytosine and 5- methylcytosine. One of the best-known roles for these DNA methyltransferases is to protect the host genome against the restriction enzymes they encode to serve as defense systems against bacteriophages. Other well-documented roles include DNA mismatch repair (e.g. the Dam methylase in *Escherichia coli*) and cell cycle control (e.g. M.CcrI in *Caulobacter crescentus*). Recently, a DNA methyltransferase has been shown to control sporulation in *Clostridium difficile*. Recent sequencing of bacterial genomes has shown that a large number contain orphan DNA methyltransferases with no currently known biological function. There are clearly many new functions to be discovered and in this talk I will give an overview of this fascinating field.

ROLE OF HYPOXIA-INDUCIBLE FACTORS IN OXYGEN HOMEOSTASIS AND CANCER PROGRESSION

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Hypoxia-inducible factors (HIFs) are transcriptional activators that balance O2 supply and demand by regulating the expression of genes that control the delivery and consumption of O2, respectively. We purified HIF-1 and found that it was a heterodimer composed of an O2-regulated HIF-1alpha subunit and a constitutively expressed HIF-1beta subunit. In the presence of O2, HIF-1alpha is subject to hydroxylation on two proline residues. Hydroxylated HIF-1alpha is bound by the von Hippel-Lindau protein (VHL), which recruits a ubiquitin-protein ligase complex, leading the ubiquitination and proteasomal degradation of HIF- 1alpha under normoxic conditions. Under hypoxic conditions, hydroxylation is inhibited leading to the rapid accumulation of HIF-1alpha, dimerization with HIF-1beta, binding to hypoxia response elements, and transcriptional activation of target genes. HIF-2alpha and HIF-3alpha are also O2-regulated and dimerize with HIF-1beta, but unlike the ubiquitous expression of HIF-1alpha, they are only expressed in a limited number of cell types. We now know of over 8,000 mRNAs, miRNAs, and lncRNAs which are directly activated by HIFs in response to hypoxia in one cell type or another. The HIF system is coopted by cancers to facilitate tumor angiogenesis, metabolic reprogramming, immune evasion, cancer stem cell specification, invasion and metastasis. Increased HIF-1a protein in the diagnostic tumor biopsy is associated with patient mortality in brain, breast, cervical, colorectal, endometrial, gastric, hepatocellular, lung, oropharyngeal, ovarian, pancreatic, and prostate cancer. We have identified a small molecule HIF inhibitor that blocks hepatocellular cancer growth and improves the response to anti-PD1 immunotherapy in mouse models by switching the tumor immune microenvironment from one that is immunosuppressive to one that promotes anti-tumor immunity.