be concluded that priorities have to be set, expectations have to be supported by reliable data, interpretations that are not considered are the true risks of prevention, well-supported theoretical considerations are the cut diamonds of prevention, and practical considerations will unfold from a good theory.

Session 2. Cancer Prevention: The Scientific Base

S4
Genetics in cancer prevention

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Genetics has enabled us to identify individuals at remarkably high risk of specific cancers. Some of this information can be used to distinguish individuals with high cancer risk who can consider cancer risk-reducing interventions too invasive for the rest of the population, including prophylactic surgical removal of organs at risk, and intensified surveillance to direct resection of premalignant lesions. Genetic information can also identify individuals who do not share the increased risk with relatives, and can avoid invasive measures. Epidemiologic data can identify specific exposures that can modify inherited cancer risk. Examples would include the earlier age at onset of lung cancers among Li Fraumeni (p53 mutation) family members who smoke cigarettes, and the reduction in breast cancer risk among BRCA1/2 family members who exercise. One issue is whether the biology of tumors that develop in the setting of inherited susceptibility is different from that of the sporadic cancers of that organ, so that targeted mechanisms of risk reduction cannot be generalized to the larger population. Alternatively, if inherited cancers are more accelerated versions of malignant development along the standard pathway, then study of genetic risk populations should lead to faster development of risk reduction interventions. Examples will be discussed.

S5
Biomarkers for early detection and as surrogate endpoints in cancer prevention trials: issues and opportunities

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In order to improve the early detection and diagnosis of cancer, give more accurate prognoses, stratify individuals by risk, predict response to treatment, and help the transition of basic research into clinical application, biomarkers are needed that accurately represent or predict clinical outcomes. To be useful in trials for chemopreventive agent development, biomarkers must be subject to modulation, easy to obtain and quantify, and have biological meaning, ideally representing steps in well-understood carcinogenic pathways. Though difficult to validate fully, wisely chosen biomarkers in early-phase trials can inform the prioritization of large-scale, long-term trials that measure clinical outcomes. When well-designed, smaller trials using biomarkers as surrogate endpoints should promote faster decisions regarding which targeted preventive agents to pursue, promising greater progress in the personalization of medicine. Biomarkers could become useful in distinguishing indolent from aggressive forms of ductal carcinoma in situ as well as localized invasive breast and prostate cancer, lesions that are often overtreated. Chemopreventive strategies that reduce the progression of early forms of pre-malignancy can benefit patients not only by reducing their risk of cancer and death from cancer but by reducing their need for invasive interventions. Genomic and proteomic methods offer the possibility of revealing new potential markers, especially for diseases whose biology is complex or not well understood. Panels of markers may be used to accommodate the molecular heterogeneity of cancers. Biomarkers in phase 2 prevention trials of combinations of chemopreventive drugs have been used to demonstrate synergistic action of multiple agents, allowing use of lower doses, with less toxicity, a critical feature of interventions intended for cancer prevention.

S6
Targeting polyamines and inflammation for cancer prevention

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Increased polyamine synthesis and inflammation have long been associated with intraepithelial neoplasia, which are risk factors for cancer development in humans (Gerner and Meyskens, Clinical Cancer Research 15: 758–61, 2009). Both experimental and clinical studies suggest that polyamines may be involved in inflammatory processes in several tissues. Genetic epidemiology results indicate that a single nucleotide polymorphism influencing the expression of a polyamine biosynthetic gene is associated with risk of colon and prostate cancers. This genetic variant is also predictive of response to aspirin as a colon adenoma preventive agent. A prospective, randomized, placebo-controlled clinical trial of difluoromethylornithine (DFMO), a selective inhibitor of polyamine synthesis, showed that the one year treatment duration reduced prostate volume and serum prostate-specific antigen (PSA) doubling time in men with a family history of prostate cancer (Simoneau et al Cancer Epidemiology, Biomarkers and Prevention 17: 292–9, 2008). This trial also provided anecdotal evidence for suppression of prostate cancer progression. A second, randomized, placebo-controlled clinical trial of DFMO in combination with sulindac, a nonsteroidal anti-inflammatory drug in patients with prior colon polyps found that the three-year treatment was associated with a 70% reduction of all, and over a 90% reduction of advanced and/or multiple metachronous colon adenomas (Meyskens et al Cancer Prevention Research 1: 32–38, 2008). Treatment-associated toxicities were rare and associated with pre-treatment clinical and genetic risk factors. This latter proof-of-principle trial indicates that targeting polyamine synthesis and inflammation can be an effective strategy for reducing risk factors, such as colon adenomas, that are closely associated with the development of colon cancers in humans. This strategy may be applicable for reduction of risk factors for other human cancers.

S7
Thinking about the role (largely ignored) of heavy metals in cancer prevention: chromium and melanoma as a case in point

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Session 3. Infection and Cancer Prevention: Hepatitis and *H. pylori*

S8
Hepatitis B virus and cancer prevention

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Chronic infection of a virus of bacteria may closely relate to carcinogenesis. Chronic Hepatitis B virus (HBV) infection can cause liver inflammation, injury and regeneration (chronic hepatitis, liver cirrhosis), and lead to hepatocellular carcinoma (HCC). HBV is the world most common etiologic

agent of liver cancer, particularly in high prevalence areas for liver cancer, while HCC is one the five major cancers globally. The world first universal HBV vaccination program was launched in Taiwan in 1984. The prevalence of HBV infection has been reduced remarkably to approximately one tenth of the original prevalence after the vaccination program. Further more, reduction of the HCC incidence in children aged 6–14 years have been demonstrated in the vaccinated birth cohorts. Recently we have further provided evidence that the effect of HCC prevention by universal HBV immunization program has been extended from childhood to early adulthood. The risk of developing HCC in HBV vaccinees was associated with incomplete HBV vaccination; prenatal maternal HBsAg seropositivity and HBeAg seropositivity. Failure to prevent HCC results mostly from unsuccessful control of HBV infection by highly infectious mothers. Future strategies to increase the global coverage rate of HBV immunization and to interrupt mother-to-infant transmission may further enhance the cancer prevention effect of HBV immunization. Successful prevention of chronic hepatitis B virus (HBV) infection can reduce the incidence of liver cancer. It is the first example of cancer preventive vaccine in human, which proves that prevention of the infection of an infectious agent can prevent its related cancer.

S9

Prevention of hepatocellular carcinoma in chronic hepatitis C infection

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Chronic infection with the hepatitis C virus (HCV) can lead to cirrhosis and hepatocellular carcinoma (HCC). HCV infection is found worldwide, with a prevalence of approximately 1-3% and an estimated total disease burden of more than 150 million persons. Studies in Asia, Europe and North America report a 1–4% annual incidence of HCC among subjects with HCV cirrhosis. In the USA, the incidence of hepatocellular carcinoma has doubled in the past 30 years and is expected to increase further in the next decade. Progression of liver disease among subjects infected with HCV in the 1960s to 1990s as a result of percutaneous exposure is the leading reason for the increase in HCC. Prevention of HCV-induced HCC could occur by: (1) prevention of HCV infection, (2) curative treatment of patients infected with HCV, and (3) chemoprevention among patients in whom HCV infection could not be cured. At present, there is no vaccine to prevent HCV infection. Fortunately, the incidence of HCV in the United States has decreased by more than 90% over the past 2 decades. Also, during the past 20 years scientists have found treatments to cure chronic hepatitis C infection. Studies in Japan, Europe and North America have reported that curing HCV infection through treatment with interferon and ribavirin reduces the risk of HCC by 70–90%. Regrettably, many patients with HCV infection are not candidates for treatment, or have failed to be cured with interferon/ribavirin. Several large clinical trials have tested the efficacy of chronic, low-dose interferon treatment in the prevention of HCC in the belief that suppression of HCV may reduce HCC risk; unfortunately, the results of these studies have been negative. Non-antiviral chemopreventive trials are in progress. Based on animal studies showing efficacy in preventing chemical hepatocarcinogenesis, the National Cancer Institute (USA) has funded a Phase IIa trial to determine whether S-adenosylmethionine (SAMe, AdoMet) is effective in reducing alpha fetoprotein (AFP; a tumor marker for HCC) in patients with HCV cirrhosis. The future of HCC prevention in HCV will likely test HCV protease inhibitors and HCV polymerase inhibitors, two classes of drugs which are remarkably effective in curing HCV infection in Phase II trials. Because of the cost and potential side effects of HCV protease and polymerase inhibitors, it is hoped that non-antiviral drugs which are safe, inexpensive and effective in preventing HCC can be found.

S10

Studies on *H. pylori* infection and risk for gastric cancer in Latin-American countries

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Inflammation as a driving force for the development of preneoplastic lesion is clearly exemplified in the case of gastric cancer and infection with *Helicobacter pylori*. *H. pylori* colonizes the gastric mucosa of humans early in life establishing an unusual long-lasting chronic inflammation of the mucosa. After decades of continuous dialogue bacteria-host, in some cases balance is broken leading to diseases, the more severe being gastric cancer. Aggressive bacterial products add to the potentially harmful uncontrolled inflammatory mediators to damage epithelia. Reactive oxygen and nitrate compounds produced by activated inflammatory cells would also threaten DNA stability. Risk to develop gastric cancer is multifactorial and genetics of both, the host and the bacteria are important, as are other environmental factors such as diet or habits. All this factors vary from country to country and between different ethnic groups. Latin-American countries constitute a mosaic of humans groups with different genetic background and in consequence a mosaic of genetically diverse *H. pylori* strains. Thus, it is not surprising to observe Latin-American countries with the highest world mortality rates like Chile or Colombia and countries with low rates such as Mexico or Argentina. Differences in rates of *H. pylori* infection does not explain the differences in GC mortality as in most Latin-American countries prevalence in adults is over 80%, including Mexico or Colombia. We have found sequence differences in genes associated with virulence such as cagA or vacA that may partially explain their differential carcinogenic potential. Regarding areas of high risk (mountains) versus low risk (coasts) in countries such as Colombia, the presence of cagA gene and of the vacA s1m1 isotype have been found more frequently in areas with high GC risk. *H. pylori* strains from high risk areas have also shown to induce higher levels of oxidative and nitrosative reactive compounds from inflammatory cells. Regarding human genetics, our studies in Mexico and Paraguay suggest polymorphisms in genes of the innate and inflammatory responses such TLRs, HLA or TNF may increase the risk for gastric cancer. Polymorphisms in IL-1 have been reported associated with GC in some Latin-American countries but not in others. As for environmental factors, whereas consumption of cola-soda and smoking increase risk, eating vegetables or fruits rich in antioxidants have shown some protection and regression of early precancerous lesions. Whereas *H. pylori* infection is considered the principal cause for GC, this infection is not enough to cause disease and studies on the host and his environment are also necessary to better define groups at risk for GC.

Session 4. Prevention of Prostate Cancer: PSA-Screening and beyond

S11

Nutritional aspects of primary prostate cancer prevention

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There are three well-known and indisputable risk factors for development of prostate cancer, namely heredity, ethnic origin and increasing age. Geographic variations in incidence rates are considerable and, therefore, it has been suggested that environmental factors may also play a role. Data from