Targeting Clonal Neoantigens

In a study e-published on March 3 ahead of print in *Science*, McGranahan, from University College London (UK), and researchers from the UK, Germany, and the United States reported on the observed effects of neoantigen intratumor heterogeneity on antitumor immunity, with specific findings on clonal neoantigen burden and overall survival in patients with lung cancer. The study was widely covered in the popular and scientific press as a breakthrough toward understanding differential responses to checkpoint inhibitor and other targeted cancer therapies. In complex and multistage investigations of evolving neoantigen heterogeneity in tumor growth, the authors identified a relationship between clonal neoantigen burden and overall survival in primary lung adenocarcinomas. Additional data suggested that the high clonal neoantigen burden observed in lung adenocarcinoma is associated with an inflamed tumor microenvironment and activated effector T cells. The reactivity of $CD8^+$ tumor-infiltrating lymphocytes to clonal neoantigens was investigated in early-stage non–small cell lung cancer (NSCLC), with results indicating the potential of clonal neoantigens to promote priming and infiltration by neoantigen-reactive T cells expressing high levels of programmed cell death protein-1 (PD-1). Additional studies in patient groups with advanced NSCLC and melanoma found that sensitivity to PD-1 and cytotoxic T-lymphocyte–associated antigen-4 blockade was enhanced in tumors enriched for clonal neoantigens and that T cells recognizing clonal neoantigens were detectable in patients and associated with durable clinical benefit. The authors concluded that "identification of cytotoxic tumor-infiltrating T cells recognizing clonal mutations, shared by all tumor cells, might hold promise for adoptive therapy strategies to address the challenges of intratumor heterogeneity" and that the "extensive clonal mutational repertoire present in smoking-associated NSCLC could render this disease vulnerable to vaccination or T cell therapies targeting multiple clonal neoantigens, in combination with appropriate immune checkpoint modulation."

Science

North American Nuclear Medicine Market Predictions

The North American nuclear medicine market is expected to grow to US $2.98 billion in 2020 from $1.97 billion in 2015, representing a compound annual growth rate of 8.6%, according to a report released on March 16 by industry analyst Research and Markets (Dublin, Ireland). The report, *North American Nuclear Medicine/Radiopharmaceuticals Market—Forecasts to 2020*, cites drivers such as increasing preference for SPECT and PET, growth in α-particle radioimmunotherapy–based cancer treatments, advances in radiotracers, rising incidences of cancer and cardiovascular disease, and enhanced awareness about the effective use of radiopharmaceuticals in various applications. However, factors such as requirements for high capital investments for procurement of scanners, shorter half-lives of radiopharmaceuticals, stringent regulatory guidelines and requirements for Good Manufacturing Practice, and competition from conventional diagnostic procedures may challenge growth in this market.

Radioisotopes in development, alternative diagnostic radiopharmaceutical solutions, cyclotron-based production, and use of radiopharmaceuticals in neurologic applications were all cited as potential elements in future nuclear medicine market growth. Also cited were substantial efforts toward domestic production of ^{99}Mo and approval of new radiopharmaceuticals by the U.S. Food and Drug Administration. The report is available through http://www.researchandmarkets.com/research/3p5j47/north_american.

Research and Markets

High CAC and Noncardiovascular Disease

In a study published online on March 3 ahead of print in the *Journal of the American College of Cardiology: Cardiovascular Imaging*, Handy, from the Johns Hopkins Ciccarone Center for the Prevention of Heart Disease (Baltimore, MD), and a consortium of participating researchers from the Multi-Ethnic Study of Atherosclerosis (MESA) reported on the association of coronary artery calcium (CAC) scores with noncardiovascular disease. The study included data from MESA 6,814 participants followed for a median of 10.2 y, during which time 1,238 were diagnosed with 1 or more noncardiovascular diseases. The researchers looked at the relationship between CAC scores and increased risk of new diagnoses of cancer, pneumonia, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), deep vein thrombosis/pulmonary embolism, hip fracture, and dementia during this period. Of those participants with CAC scores >400, 36.9% were diagnosed with a noncardiovascular disease, compared with only 11% of participants with no CAC. Results showed that participants with elevated CAC scores were at increased risk for cancer, CKD, COPD, and hip fracture. Those with CAC = 0 were less likely to develop common age-related comorbid conditions, representing a population the researchers called "healthy agers."

"Plaque in the arteries is the result of cumulative damage and inflammation, and vulnerability to injury and chronic inflammation likely contributes to diseases like cancer, kidney and lung diseases, as well as cardiovascular disease. So it makes sense that the coronary calcium score—a measure of arterial aging—is predictive of noncardiovascular diseases, too," said senior author Michael Blaha, MD, MPH, in a Johns Hopkins press release. "The reason the coronary calcium score may work so well at identifying vulnerability to a

variety of chronic diseases is because it's a direct measurement of the cumulative effect of all risk factors, rather than a consideration of a single risk factor, like obesity, smoking or high blood pressure." The authors cautioned that the results of their association study neither targeted nor found causal relationships between CAC levels and specific noncardiovascular diseases. These relationships remain to be explored.

Johns Hopkins University
JACC. Cardiovascular Imaging

Sex, Verbal Skills, and Early AD

Women may retain word memory skills better than those of men despite evidence of similar levels of shrinkage in areas of the brain that show the earliest signs of Alzheimer disease (AD), according to a study published on March 16 ahead of print in *Neurology.* The study looked at sex differences in verbal memory deficits and neurodegeneration (assessed as hippocampal-to-intracranial volume ratio) in 379 healthy participants, 694 participants with amnestic mild cognitive impairment, and 235 participants with AD and dementia. Participants had undergone clinical and cognitive evaluations, including a verbal episodic memory assessment. Cross-sectional data on each patient were extracted from the Alzheimer's Disease Neuroimaging Initiative database. The authors found that women performed better than men on tests of both immediate recall and delayed recall among those showing evidence of minimal-to-moderate amounts of hippocampal shrinkage. At the highest level of hippocampal shrinkage, no sex differences were noted. At the score that indicated the start of verbal memory impairment (37 on a scale of 0–75 for immediate recall), women showed greater evidence of hippocampal shrinkage but still outperformed men on the verbal memory assessment.

"One way to interpret the results is that because women have better verbal memory skills than men throughout life, women have a buffer of protection against loss of verbal memory before the effects of AD kick in," said lead author Erin E. Sundermann, PhD, of Albert Einstein College of Medicine (Bronx, NY) in a related press release. "Because verbal memory tests are used to diagnose people with AD and its precursor, mild cognitive impairment, these tests may fail to detect mild cognitive impairment and AD in women until they are further along in the disease." Mary Sano, PhD, from the Icahn School of Medicine at Mount Sinai (New York, NY) noted in a related editorial in *Neurology* that, "At a public policy level, the potential health care cost for underdetection or delayed diagnosis of women with AD or its early stages is staggering and should motivate funding in this area. If these results are confirmed, then we may need to adjust memory tests to account for the difference between men and women in order to improve our accuracy in diagnosis."

Neurology
American Academy of Neurology

Periodontal Disease and AD

Results of a study published on March 10 in the online journal *PLOS ONE* (2016;11:e0151081) suggested that gum disease in elderly patients may be associated with faster cognitive decline in Alzheimer disease (AD). The report, by Ide, from King's College London and Guy's Hospital (London, UK), and researchers from a consortium of UK centers, focused on 60 participants with mild-to-moderate AD who were assessed over a 6-mo period for periodontitis, cognitive changes, and systemic serum inflammatory markers. The presence of periodontitis at baseline assessment was not related to cognitive status; however, periodontitis was associated at 6-mo assessment with a 6-fold increase in the rate of cognitive decline. Inflammatory markers were increased as well, although no causal relationship was documented. The authors noted that declines in dental health in individuals with cognitive impairment are often attributed to an inability to follow through with adequate dental hygiene and/or professional care. The question of whether gum disease, with accompanying chronic low-grade inflammation, may itself speed cognitive decline remains to be explored.

PLOS ONE

2016 Henkin Fellows Named

SNMMI and the Education and Research Foundation for Nuclear Medicine and Molecular Imaging announced on March 1 that Thomas Hope, MD, and Prashant Jolepalem, MD, are the recipients of the 2016 Robert E. Henkin Government Relations Fellowship. Each year, the recipients travel to Washington, DC, and spend a week with SNMMI staff, visiting Congress, federal agencies, and other medical/professional societies. Hope is an assistant professor at the Department of Radiology and Biomedical Imaging at the University of California San Francisco. He has worked extensively with ^{68}Ga-labeled agents through the U.S. Food and Drug Administration (FDA) development pipeline. He plans to use the Henkin fellowship to explore the challenges and processes of FDA approval of radiotracers. Jolepalem is a nuclear medicine physician at the William Beaumont Health System (Royal Oak, MI) and the Westchester PET and Medical Imaging facility (Hawthorne, NY). He received his medical degree from St. Matthew's University School of Medicine (Grand Cayman, British West Indies) in 2009. His areas of expertise include PET, CT, and SPECT/CT. He indicated that he wants to use the Henkin fellowship to become a "physician statesman" to create a more involved physician group to advocate for more sustainable and beneficial health care policies. The fellowship is made possible by a contribution from Robert E. Henkin, MD.

Thomas Hope, MD

Prashant Jolepalem, MD

SNMMI