Intramural Continuing Umbrella of Research Experiences

WELCOME CEREMONY

FRIDAY, OCTOBER 13, 2023

NIH NATIONAL CANCER INSTITUTE

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

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"The iCURE program has enormous potential for identifying and training outstanding scientists from underrepresented minorities."

— Douglas R. Lowy, MD, NCI Principal Deputy Director

"The iCURE program provides a unique opportunity for trainees to have a challenging and rewarding research experience and be mentored for a future career in cancer research. The scholars equally enrich NCI through their interests, passions, and perspectives."

— Dinah S. Singer, PhD, Deputy Director, NCI Scientific Strategy and Development

"We are excited to expand the highly successful extramural CURE program into the intramural community. iCURE scholars will gain a valuable research experience and an understanding of how to navigate an NIH intramural research career path—and, in the process, they will help enrich the intramural environment."

— Sanya A. Springfield, PhD, CRCHD Director

"We are looking forward to welcoming a diverse group of highly talented iCURE students and postdocs to our laboratories. Diversity of thought and culture is essential for the innovative and creative environment we pride ourselves on in the NCI intramural program."

— Tom Misteli, PhD, CCR Director

"We have been fortunate to have an increasing number of iCURE scholars coming to DCEG. Diversity—of background, thought, and approach—improves the scientific community and the quality and impact of our research. Our trainees work collaboratively with DCEG's investigators to uncover the causes of cancer in human populations."

— Stephen J. Chanock, MD, DCEG Director

"Our Division offers a unique and robust training experience for cancer research trainees with a focus on cancer control and an emphasis on health equity and health disparities. Our outstanding mentors are experienced in working with trainees from diverse backgrounds and offer a range of topics to explore. Do consider joining us."

— Katrina A. B. Goddard, PhD, DCCPS Director

AGENDA

2023 iCURE WELCOME CEREMONY

October 13, 2023, 2:00 – 4:30 p.m. EDT

NIH Bethesda, Building 35A, Rooms 610/620/630

2:00 – 2:05 p.m.	**Opening Remarks** **Dr. Jessica Calzola**, iCURE Program Director NCI Center to Reduce Cancer Health Disparities
2:05 – 2:20 p.m.	**Welcome to NCI** **Dr. Glenn Merlino**, Scientific Director for Basic Research, NCI Center for Cancer Research **Dr. Stephen Chanock**, Director, NCI Division of Cancer Epidemiology and Genetics **Dr. Katrina Goddard**, Director, NCI Division of Cancer Control and Population Sciences
2:20 – 2:30 p.m.	**Chapter 6: iCURE 2023**
2:30 – 2:40 p.m.	**Perspectives from an iCURE Alum** Introduction by **Dr. John Fenimore**, iCURE Postdoctoral Scholar **Ms. Garis Grant,** PhD Candidate, University of Maryland Baltimore, Cohort 3 iCURE Scholar Alumni
2:40 – 2:55 p.m.	**Keynote Speaker** Introduction by **Dr. Jeyshka Reyes González**, iCURE Postdoctoral Scholar **Dr. Troy McEachron**, NIH Distinguished Scholar, Investigator, Pediatric Oncology Branch, NCI Center for Cancer Research
2:55 – 3:00 p.m.	**Closing Remarks** **Dr. H. Nelson Aguila**, Deputy Director, NCI Center to Reduce Cancer Health Disparities
3:15 – 4:30 p.m.	**Networking Poster Session and Reception** Meet the newest cohort of scholars at their posters. Continuing scholars also will present scientific posters. New and continuing scholars will be at their posters during the times noted below: **3:15 – 3:35 p.m.: Atuahene Adu-Gyamfi, Dr. Quiera Booker, Macy Corley, Dr. Tara Davis, Dr. Whitney Do, Mahider Enyew, Dr. Toluleke Famuyiwa, Dr. Annie Gilbert, Erika Kaschak, Michael Kebede, and Maya Larbi** **3:40 – 4:10 p.m.: Mona Miraftab, Paloma Mitra, Dr. Christine Muli, Dr. Stephanie Pitts, Dr. Jeyshka Reyes González, Dr. Ashlie Santaliz Casiano, Erica Stephens, Jade Witter, Dr. Corey Young, and Amy Yu** **Light refreshments will be served during the Networking Poster Session and Reception.*

2023 iCURE Scholars

Atuahene Adu-Gyamfi

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Macy Corley

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Lisa Boxer, PhD
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Erica Stephens

Aimée Kreimer, PhD
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Jade Witter

Eugene Valkov, DPhil
RNA Biology Laboratory
CCR Frederick

Amy Yu

Christine Heske, MD
Pediatric Oncology Branch
CCR Bethesda

KEYNOTE SPEAKER

DR. TROY MCEACHRON

Investigator, Pediatric Oncology Branch
NCI Center for Cancer Research

Dr. McEachron earned his doctorate in molecular and cellular pathology from the University of North Carolina at Chapel Hill in 2011. He completed postdoctoral fellowships at St. Jude Children's Research Hospital and at the Translational Genomics Research Institute. In 2016, Dr. McEachron joined the faculty of the Keck School of Medicine at the University of Southern California as an assistant professor in the Department of Translational Genomics (primary appointment) and the Department of Pediatrics (secondary appointment). Dr. McEachron joined the Pediatric Oncology Branch in 2021.

Dr. McEachron has been the recipient of various fellowships and awards including the Minority Access to Research Careers Fellowship, the AACR Minority Scholar in Cancer Research Award, the Ruth L. Kirschstein National Research Service Award Predoctoral Fellowship, the UNCF/Merck Postdoctoral Science Research Fellowship, the AACR Minority and Minority-serving Institution Faculty Scholar in Cancer Research Award, and the Thermo Fisher Scientific Cancer Research Award. Dr. McEachron has also received grant funding from NCI, the Concern Foundation, STOP Cancer, and the American Cancer Society.

Abstract List

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   Author: Corey Young

Abstracts

1: Pan-Viral Serology Uncovers Distinct Virome Patterns Among Hepatocellular Carcinoma and Control Populations

AUTHORS: Do, W. L.[1], Wang, L.[1], Forgues, M.[1], Jinping Liu, J.[1], Rabibhadana, S.[2], Pupacdi, B.[2], Chaisaingmongkol, J.[2], Bhudhisawasdi, V.[3], Pairojkul, C.[3], Sukeepaisalkul, W.[3], Pugkhem, A.[3], Luvira, V.[3], Lertprasertsuke, N.[4], Chotirosniramit, A.[4], Auewarakul, C. U.[5], Ungtrakul, U.[5], Sricharunrat, T.[5], Sangrajrang, S.[6], Phornphutkul, K.[7], Budhu, A.[1,8], Harris, C. C.[1], Mahidol, C.[2], Ruchirawat, M.[1,9], Wang, X. W.[1,8,10]

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BACKGROUND:

This study evaluates the pan-serological profiles of hepatocellular carcinoma (HCC) compared to several diseased and non-diseased control populations to identify novel risk factors and biomarkers of liver cancer.

METHODS:

Data derived from a Thai case-control study including individuals with HCC (n=663), chronic liver disease (CLD, n=199), and healthy population controls (PC, n=686). We used VirScan to screen patient serum samples for exposure to over 1280 strains of pathogenic and non-pathogenic viruses and develop a model discriminating HCC from PC using the XGBoost algorithm. Viral peptides which were differential between HCC and PC were further integrated with tumor mRNA expression data using trans-kingdom network analysis.

RESULTS:

We found 46 viral features which differentially discriminated HCC from PC. Integrating these features into a viral score showed differential enrichment across all populations adjusting for biological and lifestyle confounders. When examining the utility of the viral score in the at-risk population (CLD), we found the viral score was positively associated with several liver function markers (all $p<0.05$) and was also predictive of all-cause mortality (HR: 2.01, 95% CI: 1.06, 3.82), though clinical HCV and HBV were not predictive. Integrating the viral peptides with mRNA, the largest cluster included 406 peptides and 62 genes. Enriched pathways included innate and humoral immune response, killing of cells of another organism, and antimicrobial humoral response.

CONCLUSION:

Our studies indicate that both hepatitis and non-hepatitis viral exposures were able to distinguish HCC from control populations. Using an aggregate 46 viral feature score, we found improved utility of the viral score at determining clinical risk and mortality in CLD patients compared to clinical hepatitis status. Finally, differential viral peptides clustered with immune response genes which may play a role in tumorigenesis.

FUNDING:

This work was supported in part by grants (Z01 BC 010877, Z01 BC 010876, Z01 BC 010313, and ZIA BC 011870) from the intramural research program of the Center for Cancer Research, National Cancer Institute of the United States to X.W.W.

Abstracts

2: Characteristics of Extra Endocrine Features in a Cohort of Patients with MEN2B Seen at the NIH

AUTHORS: Enyew, M.[1], Hogan, J.[1], Akshintala, S.[1], Acosta, M. T.[2], Glod, J.[1]

[1]Pediatric Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD; [2]Undiagnosed Disease Program, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD

BACKGROUND:

Multiple endocrine neoplasia type 2B (MEN2B) is a rare autosomal dominant cancer predisposition syndrome caused by an activating germline mutation of the rearranged during transfection (RET) proto-oncogene (typically p.M918T). MEN2B is associated with 100% risk of medullary thyroid carcinoma (MTC), and approximately 50% lifetime risk of pheochromocytoma (PHEO). Mucosal ganglioneuromas, marfanoid habitus, gastrointestinal and musculoskeletal manifestations are common non-tumor manifestations of MEN2B syndrome.

OBJECTIVES:

To characterize the tumor and non-tumor features of MEN2B patients followed at the National Institutes of Health (NIH).

METHODS:

We analyzed the clinical data including physical exams, laboratory examinations, and imaging findings collected up to January 2023 for 55 patients with MEN2B followed at the NIH. Patients were enrolled in either the natural history study of children and adults with MEN2 (NCT01660984) or the natural history and biospecimen acquisition study for children and adults with rare solid tumors (NCT03739827). Occurrence of non-tumor manifestations, PHEO, and MTC were assessed.

RESULTS:

Age at diagnosis of MEN2B ranged from <1 year to 30 years old (median of 10 years). Skeletal, gastrointestinal, and genitourinary manifestations were common in our population with 53 patients (96.4%) having neurological manifestations, forty-seven patients (85.5%) had skeletal features of MEN2B, all 55 patients (100%) had gastrointestinal symptoms, and 45 patients (81.8%) had genitourinary findings.

CONCLUSION:

In addition to well-characterized extra-endocrine manifestations of MEN2B, patients with this syndrome may also have neurological, gastrointestinal, and genitourinary issues. Recognition of these features of MEN2B may facilitate earlier diagnosis of patients with this rare syndrome.

Abstracts

3: *In Vivo* Detection of HIV-1 Antisense Transcripts in Donors Before and During ART

AUTHORS: Famuyiwa, T. O.[1], Capoferri, A. A.[1], Sklutuis, R.[1], Pathak, S.[1], Groebner, J. L.[1], Li, R.[2], Rausch, J. W.[1], Deeks, S. G.[3], Mellors, J. W.[4], Coffin, J. M.[5], Romerio, F.[2], Kearney, M. F.[1]

[1]HIV Dynamics and Replication Program, National Cancer Institute, Frederick, MD; [2]Department of Molecular and Comparative Pathobiology, The Johns Hopkins University School of Medicine, Baltimore, MD; [3]University of California San Francisco, San Francisco, CA; [4]Department of Infectious Diseases, University of Pittsburgh, Pittsburgh, PA; [5]Department of Molecular Biology and Microbiology, Tufts University, Boston, MA

BACKGROUND:

Antisense transcripts (AST) was demonstrated to promote HIV latency through epigenetic modification of histones in the 5' LTR by the Polycomb Repressor Complex 2 (PRC2). Here, we asked whether HIV AST is expressed in infected PBMCs collected from untreated and ART-treated donors.

METHODS:

AST levels were measured by cell-associated antisense RNA single-genome sequencing (SGS) of a 1.7kb fragment in the opposite orientation of the env coding region. An endpoint digital PCR approach with tagged-cDNA and donor-specific primers was also used to quantify AST copies in the samples.

RESULTS:

We detected HIV AST in 11/12 donors with a median of 14 [IQR 5-34] copies/100 infected PBMCs. Antisense SGS revealed that about 5% of infected PBMCs collected from donors on ART contained AST at any given time. Digital PCR showed similar levels of AST expression in untreated donors with varying levels of plasma viremia. Further, in the donors on ART, we observed no statistical difference between the levels of sense and antisense transcripts.

CONCLUSION:

HIV antisense transcripts are expressed at low levels in both ART-treated and untreated individuals. The *in vivo* expression of AST irrespective of treatment status warrants further investigation into its potential role as a long non-coding RNA capable of regulating HIV-1 sense gene expression and inducing HIV latency. Understanding the role of HIV AST *in vivo* may inform future strategies for controlling HIV replication without ART.

Abstracts

4: Identification of lncRNA Binders to Investigate Chromosome Instability in Cancer

AUTHORS: Gilbert, A. K.[1], Yang, M.[2], Arunkumar, G.[1], Schneekloth Jr., J. S.[2], Dalal, Y.[1]

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Centromeric protein A (CENP-A) is a histone H3 variant overexpressed in several cancers. CENP-A is an essential protein for recruiting microtubule attachment to the centromere which ensures proper segregation of chromosomes during cell division. In cancer cells, excess CENP-A is deposited ectopically at fragile chromosomal sites leading to mitotic defects. Recent work shows that non-centromeric H3.3 chaperones work with an 8q24 locus-derived lncRNA (PCAT2) to mediate mislocalization of CENP-A to the 8q24 locus in colon cancer cells. The 8q24 locus is translocated and amplified in several cancers and is associated with low survival. We hypothesize the CENP-A mislocalization pathway at the 8q24 locus could be a promising therapeutic target to disrupt cancer progression. In this work, we are performing a small molecule screen to target CENP-A and lncRNA-chaperone complexes to regulate the ectopic deposition of CENP-A. To achieve an effective screen, we first identify PCAT2 binding protein targets using chromatin immunoprecipitation (ChIP) and RNA pulldown experiments. Then, we synthesize fluorescently labeled PCAT2 RNA to screen through small molecule libraries and identify selective binders. We are currently using immunofluorescence (IF) DNA Fluorescence in Situ Hybridization (FISH) to identify binders that affect CENP-A deposition at the 8q24 locus. We anticipate these small molecule RNA binders will provide a novel therapeutic route to combat cancer progression and serve as tools to probe chromosome instability caused by CENP-A mislocalization.

Abstracts

5: Longitudinal Follow-Up and Outcomes of Pediatric and Adult Patients with SDH-De icient GIST

AUTHORS: Dagalakis, U., M.D.[1], Ghabra, S., M.D.[2], Kaschak, E., B.A.[1], Ilanchezhian, M., B.S.[1], del Rivero, J., M.D.[4], Miettinen, M., M.D., Ph.D.[5], Thomas, BJ, R.N.[1], Bernstein, D., R.N., BSN[1], Raygada, M., Ph.D.[1], Flowers, C., C.R.N.P.[1], Killian, K., M.D.[6], Meltzer, P., M.D., Ph.D.[7], Reilly, K., Ph.D.[1], Wedekind-Malone, M. F., D.O.[1], Widemann, B. C., M.D.[1], Sankaran, H., M.D.[3], Blakely, A. M., M.D.[2], Glod, J., M.D., Ph.D.[1]

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BACKGROUND:

Gastrointestinal stromal tumor (GIST) are gastrointestinal non-epithelial neoplasms most commonly driven by somatic mutations in KIT or PDGFRA. Approximately ten percent of GIST are due to germline mutations in SDHx or epigenetic loss of expression of SDHC. Effective systemic therapies for SDH-deficient GIST have not yet been identified. A better understanding of the natural history of patients with these neoplasms is critical to identify effective treatments.

METHODS:

Data from patients with SDH-deficient GIST enrolled on study (NCT03739827) from January 2019 through August 2023 at the NIH were evaluated. In addition to reviewing medical records and imaging, when available, tumors were characterized by sequencing of SDH genes.

RESULTS:

Clinical information and specimens were collected from 60 GIST patients (median age at diagnosis 25, [range 7-73] years; 75% (45) female, 25% (15) male) were classified by molecular subtypes: 29.5% SDHC epimutation, 36.1% SDHA, 19.7% SDHB, 11.5% SDHC and 1.6% SDHD. Most commonly, patients had at least one surgery (58.3%) while a lower proportion had four or more (8.3%). Primary tumors occurred in the stomach with 15% having metastases at presentation the most common location being the liver (11.7%). Overall, 47.5% of patients were treated with imatinib, 21.3% were treated with sunitinib and 21.3% received other additional systemic therapies.

CONCLUSION:

Longitudinal follow-up of an SDH-deficient GIST patient cohort will allow for better understanding of the natural history including treatment history and survival of patients with this rare disease and will help to optimize strategies for treatment and follow-up of these patients.

Abstracts

6: Development of a Fluorescent-Based Assay that Monitors Proteasomal Ubiquitin Receptor Rpn10's Conformational Change with E3 Ligase E6AP

AUTHORS: Muli, C. S., Ph.D.[1], Tarasov, S. G., Ph.D.[2], Walters, K. J., Ph.D.[1]

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E3 ligases are responsible for ubiquitination of substrates for proteasomal degradation, and their activity has been therapeutically advantageous in the targeted protein degradation field with proteolysis targeting chimeras (PROTACs). We previously reported that E3 ligase E6AP binds to proteasomal ubiquitin receptor hRpn10 through E6AP's *N*–terminal zinc-binding domain (AZUL), and it's the only known proteasomal binding site of an E3 ligase thus far. To date, E3 ligases' roles at the proteasome are unknown. Therefore, we sought to develop an assay that could identify chemical probes that modulate the Rpn10/E6AP interaction. Rpn10's C-terminal domain RAZUL (Rpn10's AZUL binding domain) is poorly ordered when unbound but forms a stable helical structure when interacting with E6AP's AZUL domain. To harness this conformational phenomenon, we designed a dual-monitoring fluorescent-based assay that labels serine-to-cysteine RAZUL mutants with environmentally-sensitive fluorophores, such as acrylodan and Atto610. Acrylodan-labeled RAZUL mutants demonstrated a hypsochromic shift, yielding an increase in fluorescence intensity with the addition of AZUL. Labeling RAZUL mutants with a red-shifted fluorophore, such as Atto610, behaved in a reversed signal manner by decreasing in fluorescence intensity. With these two labeled RAZUL mutants, ($S337C^{Atto}$ and $S358C^{Acr}$) present simultaneously in a sample, we have created a robust dual-fluorophore assay with a Z' score of 0.59. We anticipate that our assay will contribute to the discovery of Rpn10/E6AP ligands, which can be used as tools to interrogate E6AP's role at Rpn10/proteasome and for E6AP-mediated PROTAC development.

Abstracts

7: Immune Correlates with Response in Patients with Metastatic Solid Tumors Treated with a Tumor Targeting Immunocytokine NHS-IL12

AUTHORS: Pitts, S. C.[1], Toney, N. J.[1], Gatti-Mays, M. E.[1], Tschernia, N. P.[1], Strauss, J.[1], Gulley, J. L.[1], Schlom, J.[1], Donahue, R. N.[1]

[1]Center for Immuno-Oncology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

BACKGROUND:

NHS-IL12 (now designated PDS0301) is a tumor-targeting immunocytokine targeting DNA/histones in necrotic areas of the tumor microenvironment. NHS-IL12 has shown promising results in preclinical studies as a monotherapy and in combination with other anti-cancer therapies such as the HDAC inhibitor Entinostat. The first-in-human clinical trial (NCT01417546) administered NHS-IL12 subcutaneously every four weeks (Q4W) and was expanded to include cohorts with bi-weekly treatment (Q2W). Here, we present immune correlates in peripheral blood to determine the impact of the dose level and schedule of NHS-IL12 on immune activation and evaluate immune correlates of clinical response.

METHODS:

Serum was evaluated for levels of cytokines/soluble factors by Elisa and Mesoscale assays, and peripheral blood mononuclear cells were assessed for 158 immune cell subsets by multicolor flow cytometry. New assays to detect soluble NK ligands and more extensively characterize the association between NK lysis and phenotype were developed in healthy donor samples.

RESULTS:

Patients treated in the Q2W cohort with a dose of 16.8 mcg/kg NHS-IL12 (versus those with 12.0 mcg/kg) exhibited greater increases in serum IFNγ, TNFα, and sPD-1, and greater increases in peripheral ki67+ mature NK, CD8+ T, and NKT cells. Greater immune activation was also seen in the Q2W versus Q4W cohort. Lower baseline levels of monocytes and plasmacytoid dendritic cells and greater increases after treatment in NK and CD8+ T cell subsets associated with improved clinical outcome.

CONCLUSION:

These findings demonstrate enhanced immune activation of both NK and T cells with higher dose levels and more frequent dosing of NHS-IL12.

KEYWORDS:

NHS-IL12, Interleukin 12, immunocytokine, immunotherapy, cancer, peripheral immunome

Abstracts

8: VLA-4-targeted Radiotherapy as Conditioning Regimen for Adoptive Cellular Therapy

AUTHORS: Reyes González, J. M., Ph.D., M.Sc.[1], Lee, W., Ph.D.[2], Okada, R., M.D., Ph.D.[1], Rajkumar, H., M.S.[3], Patel, R., M.D., Ph.D.[3], Escorcia, F. E., M.D., Ph.D.[2,4], Nguyen, R., M.D., Ph.D.[1]

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BACKGROUND:

Adoptive cell therapy (ACT) is a novel immunotherapy approach that boosts the ability of the immune system to recognize and eliminate cancerous cells. While clinical success has been observed in subsets of blood cancers, ACT has proven less effective in treating solid tumors. Unfortunately, previous attempts to overcome barriers with conventional lymphodepleting conditioning regimens have shown moderate success in improving the efficacy of ACT. In addition, associated risks of toxicities have hampered the use of nonspecific chemotherapy- and radiation-based conditioning prior to ACT. As a result, there is an urgent clinical need for the identification of optimal conditioning regimens aimed at reducing off-target toxicity and enhancing ACT responses.

OBJECTIVES:

We propose the use of targeted radionuclide therapy (TRT) to selectively deplete endogenous lymphocytes and therapeutically target tumor cells, limiting toxicity and priming the tumor microenvironment for ACT.

METHODS/RESULT:

Expression of VLA-4 integrin was confirmed in a variety of human and murine cancer cell lines by flow cytometry. LLP2A, a peptidomimetic that specifically binds VLA-4, was radiolabeled with copper-64 (^{64}Cu). Intravenous administration of ^{64}Cu-LLP2A into tumor-bearing mice followed by PET imaging and biodistribution studies showed uptake in lymphoid and tumor tissues.

CONCLUSION:

Results suggest that LLP2A is a promising peptide for TRT-based targeting of lymphoid tissues and VLA-4 expressing tumors. Our observations also support the evaluation of ^{64}Cu's theranostic partner, ^{67}Cu, labeled to LLP2A as a lymphodepleting and therapeutic agent to overcome barriers to effective ACT in solid tumors and redefine the current standard of conditioning treatment for ACT.

Abstracts

9: Investigation of Modifiable Risk Factors and Risk of Mosaic Chromosomal Alterations in the UK Biobank

AUTHORS: Young, C. D., M.S., Hubbard, A. K., Ph.D., Saint-Maurice, P., Ph.D., Khan, S. M., M.P.H., Matthews, C., Ph.D., Moore, S., Ph.D., Loftfield, E., Ph.D., Machiela, M. J., Sc.D.

Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD

BACKGROUND:

Observational studies have indicated modifiable factors such as sleep patterns, physical activity, smoking, and alcohol consumption can influence the risk of cancer. However, mechanisms underlying these relationships remain poorly understood. Clonal hematopoiesis, the clonal expansions of mutated hematopoietic progenitors characterized by mosaic chromosomal alterations (mCAs) and clonal hematopoiesis of indeterminate potential (CHIP), represent a unique opportunity to investigate the relationship between modifiable risk factors and early preneoplastic expansion of abnormal clones in the hematopoietic system.

OBJECTIVES:

In this study, we leveraged data from DNA genotyping arrays, including raw intensity and phase information, from a cohort of 485,028 participants without hematologic malignancies in the UK Biobank (UKBB) to detect two common forms of CH: mCAs and CHIP. To assess associations between self-reported patient modifiable risk factors and the risk of CH, we employed multivariable logistic regression models that were adjusted for age, sex, smoking history, and ancestry.

METHODS/RESULTS:

Our analysis identified a total of 11,826 autosomal mCAs, 15,499 instances of loss of the X chromosome (mLOX), and 43,044 instances of loss of the Y chromosome (mLOY). In terms of sleep patterns, we observed that individuals who slept for more than 9 hours had a reduced risk of mLOY compared to those who slept for 7-9 hours. Additionally, individuals who slept less than or equal to 5 hours per night also had a reduced risk of CHIP. For physical activity, we found a link between high levels of vigorous activity (e.g., more than 2 hours per day) and an increased risk of mLOY, but no such evidence was observed for autosomal mCAs, mLOX or CHIP. In the case of alcohol consumption, multiple lines of evidence suggested potential associations between alcohol intake and increased autosomal mosaicism, mLOX, mLOY and CHIP. Social deprivation scores were used to assess socioeconomic factors across various regions and communities. These scores were then subjected to testing to identify potential associations with autosomal, mLOX, mLOY mosaicism, and CHIP. Notably, among these analyses, we observed one significant association between the England social deprivation index mLOY.

CONCLUSION:

These findings offer initial insights into potential connections between modifiable risk factors and CH. Since CH serves as an intermediate marker for hematologic cancer risk, CH may shed light on specific mechanisms through which modifiable exposures contribute to overall cancer risk by promoting clonal expansion in the hematopoietic system.

iCURE Program Team

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Dr. Gregory Adams, Jr.
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