Collaboration Across Continents: Cancer Research and Training in East Africa

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Agenda

Welcome
Wafaa El-Sadr

Presentation
Edus H Warren

Q&A and Discussion

Reminders:

For questions to the panelists, use the **Q&A box**

Please use the **chat box** to indicate your name and organization

The webinar recording and slides will be posted on [www.icap.columbia.edu](http://www.icap.columbia.edu)
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Collaboration Across Continents: Cancer Research and Training in East Africa

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November 16, 2021
No conflicts of interest to disclose.
Why does the Fred Hutch do cancer research abroad?

• Opportunity to study globally important cancers that are rare or uncommon in the US, particularly *infection-related cancers*, *e.g.*,:
  - Pediatric Burkitt lymphoma in sub-Saharan Africa (SSA)
  - Kaposi sarcoma in SSA
  - Nasopharyngeal carcinoma in southern China and southeast Asia

• Need for better understanding of global heterogeneity in the genetics / genomics and biology of common cancers as well as the genomics of different populations, *e.g.:
  - Breast, lung, gastrointestinal cancers

• “Reciprocal innovation” – lessons learned abroad might have applicability to cancer care in low-resource settings in the US, *e.g.:
  - Point of care, low-cost diagnostics, oral chemotherapy regimens
Pathogen-associated cancers across the globe

Cancers attributable to infections

Proportion of cancers attributable to infections (%), by country

http://canceratlas.cancer.org/risk-factors/
Rogues’ gallery of infectious agents causing cancer

- Human Papilloma Virus
- Hepatitis B Virus
- Hepatitis C Virus
- Merkel Cell Polyomavirus
- Kaposi Sarcoma Herpes Virus
- Helicobacter pylori
- HIV
HIV-associated malignancies

- Cervical cancer – 5x risk
- Non-Hodgkin lymphoma – 70x risk
- Kaposi sarcoma – >1,000x risk
- Anal cancer
- Liver cancer
- Lung cancer
- Hodgkin lymphoma

Lurain et al., ASCO Education Book 2019
Prevalence of HIV infection across the globe

Adult HIV Prevalence, 2019

NOTE: Data are estimates. Prevalence includes adults ages 15-49
Actual and projected global population growth through 2100

Historic and projected population
Past and projections of total population from the UN’s medium fertility growth scenario.


Source: ourworldindata.org
Predicted increase in cancer incidence by HDI, 2020 – 2040

Source:
Sung et al., CA – A Cancer Journal for Clinicians
https://doi.org/10.3322/caac.21660
Total health expenditure per capita, 2018

Source: J. Dielemans, IHME
SSA countries have few trained oncology providers
Radiotherapy resources in SSA are likewise inadequate

Selected advances in medical oncology, 1997 – 2021

*WHO List of Essential Medicines, 2021
Selected advances in medical oncology, 1997 – 2021

Rituximab* 1997
Imatinib* 2001
Erlotinib* 2004
Cetuximab 2004
Ipilimumab 2011
Ibrutinib* Pembrolizumab* CAR T-cells 2013
1998
Trastuzumab*
2003
Bortezomib*
2006
HPV Vaccine*
2011
Brentuximab vedotin
2013
Trastuzumab emtansine
2014
Nivolumab* Blinatumumab
2017
2017
2021
2013
2021
*WHO List of Essential Medicines, 2021

Readily available in sub-Saharan Africa
Uganda – the “Pearl of Africa”

- Population 47.21 million in 2021 (rank: 31\textsuperscript{st} in world), growing at 3.3% annually (rank: 3\textsuperscript{rd} in world)
- Land area: 241,038 km\textsuperscript{2} – about twice that of Pennsylvania, slightly less than Oregon
- Population is 16% urban, 84% rural
- Life expectancy at birth (M/F): 60/65
- GDP per capita US$ 1,868 in 2020 (rank: 174\textsuperscript{th} in world); healthcare expenditure per capita < US$ 50
- 15% of population has access to electricity; 79% has access to “improved” water source
Uganda’s population structure: the “youth bulge”

![Population Pyramid](https://populationpyramid.net)

Population: 47,123,532

United States of America - 2021
Population: 332,915,073

**86%**

**32%**
Global cancer incidence and mortality, by site and age

Incidence

All cancers, 2016:
- 17.2 million cases
- 8.9 million deaths
- 28% increase from 2006 – 2016
  - Population growth (17%)
  - Aging (12%)
  - Decreasing age-specific incidence (-1%)

Mortality

SOURCE: The Global Burden of Disease Cancer Consortium, JAMA Oncology 2018
CURE OF BURKITT’S LYMPHOMA
Ten-year Follow-up of 157 Ugandan Patients

JOHN L. ZIEGLER
IAN T. MAGRATH
CHARLES L. M. OLWENY

Division of Cancer Treatment, National Cancer Institute,
Bethesda, Maryland 20205, U.S.A.; and
Uganda Cancer Institute, Kampala, Uganda

Summary 192 Ugandan patients with Burkitt’s lymphoma were treated with various regimens containing high-dose cyclophosphamide. 21 patients died during induction therapy, and 14 died after partial responses. Of 157 patients who responded completely to treatment, 16 were lost to follow-up (10 in remission when last seen). Of 141 evaluable responders, 69 died and 72 (51%) are alive and disease-free. 31 of the long-term survivors have relapsed at least once and have been successfully retreated. Overall, 34 surviving patients had central-nervous-system involvement, also successfully treated. It is concluded that Burkitt’s lymphoma is curable in at least 50% of patients, and that relapse and central-nervous-system involvement are not incompatible with long survival.

THE LANCET, NOVEMBER 3, 1979

Mission: advance comprehensive cancer care for Ugandans through research, high-quality evidence-based care, education, and training
• 25,000 ft² facility features outpatient clinics, laboratories, and training facilities
• Adult Kaposi sarcoma, gynecologic oncology, hematologic malignancy, and Pediatric outpatient clinics
• Operational labs: specimen processing/biorepository, BSL-2, molecular diagnostics, histopathology, sequencing
• Developing: cancer- and immuno-genomics
• Major focus of UCI – Fred Hutch collaboration: training of oncology providers (physicians and nurses) and scientists
Cancers observed at the Uganda Cancer Institute

Cancer diagnoses in all patients presenting to the Uganda Cancer Institute between June 1 and September 30, 2015 (from Bender-Ignacio, Phipps, et al., Journal of Global Oncology 2017)
Grace Mbabazi, 12-years-old, undergoing treatment for Burkitt lymphoma at UCI. Photo by Jacqueline Koch

Mary Namata, 48, being prepared for a needle biopsy at Mulago Hospital in Kampala, Dr. Constance Lehman, a radiologist at the UW-FHCRC. Photo by Lynsey Addario for NYT

Queen Mwamin, 22, is undergoing treatment for Kaposi sarcoma at the UCI. Photo by Robert Hood
BURKITT’S LYMPHOMA AND MALARIA

by

G. W. KAFUKO and D. P. BURKITT 1

East African Virus Research Institute, P.O. Box 49, Entebbe, Uganda;
and Medical Research Council Externai Staff, 172 Tottenham Court Road,
London, W.I., England

Similar distribution of holoendemic malaria and BL in Africa

Distribution of holoendemic malaria

Distribution of endemic Burkitt lymphoma

Equator
Hallmarks of Burkitt lymphoma: Epstein-Barr virus and t(MYC;Ig)

MORPHOLOGICAL AND BIOLOGICAL STUDIES ON A VIRUS IN CULTURED LYMPHOBLASTS FROM BURKITT'S LYMPHOMA

By M. A. EFSTEIN, M.D., G. HENLE, M.D., B. G. ACHONG, M.B.,B.Ch., AND Y. M. BARR

(From the Bland-Sutton Institute of Pathology, The Middlesex Hospital Medical School, London, and the Children's Hospital of Philadelphia and School of Medicine, University of Pennsylvania, Philadelphia)

PLATES 56 TO 59

(Received for publication, December 15, 1964)

Burkitt’s malignant lymphoma of children in Africa (1, 2) is of special significance because the environmental factors which govern its distribution (3, 4) suggest that causation might depend on an arthropod vector spreading an aetiological agent (2-5). Inoculation experiments with monkeys have recently provided further indications that Burkitt’s tumour might contain such a transmissible agent (6), whilst certain viruses have been found in association with a number of patients. Thus, herpes simplex has been isolated from a small proportion of biopsy specimens (7, 8) and a reovirus has been grown from biopsy material in a single instance (9). In addition, in six other cases unidentified filtrable agents have been propagated in tissue culture from various materials including tumour (10).

In the course of tissue culture experiments with samples from Burkitt lymphomas, altered lymphoblasts have been established in continuous culture from both a maxillary tumour (11, 12) and from an ovarian tumour (13, 14). These cells have the unusual ability for members of the lymphocytic series to grow in vivo in the absence of other associated cells (12-14); they also show certain fine structural features suggestive of malignancy (14, 15) and have been found, when examined in the electron microscope, to carry a virus (16, 13). So far, only the presence of this virus has been reported in preliminary notes (16, 13); in view of its possible significance in relation to the in vivo growth potential of cultured Burkitt tumour lymphoblasts, and perhaps even to the tumour itself, it was considered important to investigate further its structure and biological nature. The present communication gives a full account of the results which have been obtained.

Journal of Clinical Oncology 2000; 18:3707-3721

J. Exp. Med. 1965; 121:761-771
The global burden of Kaposi sarcoma (KS)

Estimated age-standardized mortality rates (World) in 2018, Kaposi sarcoma, both sexes, all ages

- No pre-clinical animal models
- No bona fide primary KS tumor cell lines
- Primary human cells difficult to infect with KSHV (HHV-8)
- New approaches needed to study KS in vivo at the body, tissue, cellular, and molecular levels
Kaposi sarcoma: a prototypic pathogen-associated malignancy

Identification of Herpesvirus-Like DNA Sequences in AIDS-Associated Kaposi’s Sarcoma

Yuan Chang,* Ethel Cesarman,† Melissa S. Pessin, Frank Lee, Janice Culpepper, Daniel M. Knowles,† Patrick S. Moore

Representational difference analysis was used to isolate unique sequences present in more than 90 percent of Kaposi’s sarcoma (KS) tissues obtained from patients with acquired immunodeficiency syndrome (AIDS). These sequences were not present in tissue DNA from non-AIDS patients, but were present in 15 percent of non-KS tissue DNA samples from AIDS patients. The sequences are homologous to, but distinct from, capsid and tegument protein genes of the Gammaherpesvirinae, herpesvirus saimiri and Epstein-Barr virus. These KS-associated herpesvirus-like (KSHV) sequences appear to define a new human herpesvirus.
The herpesvirus most closely related to HHV-8 is EBV.
Unlike EBV, HHV-8 seroprevalence is globally heterogeneous

From: Cesarman, Damania, Krown, et al., *Nature Reviews Disease Primer*, 2019
Subject presents to UCI with KS and is screened for enrollment

Visit 1: Study entry (pre-treatment)
- Punch biopsy of normal skin
- Punch biopsies of 2-3 KS tumors
- Oral swab
- Blood draw

Treatment: Chemotherapy +/- ART (bleomycin & vincristine; paclitaxel)

Subsequent study visits:
- Punch biopsies of 2 KS tumors
- Blood draw
- Oral swab

On-site at UCI-FHCC:
- Single-cell suspensions of KS biopsies and PBMC
- TRA & TRB sequencing of PBMC
- RT-PCR for HHV-8
- Histopathology (H & E, miHC)
- Biobanking

Off-site:
- Tumor RNAseq & Nanostring analysis
- Tumor whole exome seq (WES)
- Single-cell sequencing of KS tumors and PBMC
- TRA & TRB sequencing of KS tumors

Subjects followed for one year

“HIPPOS” Study of KS at UCI – Fred Hutch Cancer Centre

Downstream Analysis
Breast cancer studies at the UCI – FHCC

Defining the molecular profile of breast cancer in Uganda and its clinical implications

• Funded by $1.4 million award from GSK through the African NCD Open Lab Programme
• Co-Principal Investigators: Dr. Manoj Menon and Dr. Jackson Orem, with assistance from Co-Investigator Dr. Nixon Niyonzima
• Specific Aims
  • Characterize the molecular portrait and subtype prevalence of women presenting with an initial diagnosis of early stage, locally advanced, or metastatic breast cancer in Uganda.
  • Evaluate widely available molecular technology to improve the diagnosis of breast cancer in resource-limited settings.
  • Determine the feasibility of an all-oral chemotherapy regimen for treatment of locally advanced breast cancer among Ugandan women.
Adapting novel drugs to limited resource settings

- FDA approved in 1997, the anti-CD20 antibody rituximab has revolutionized the treatment of non-Hodgkin lymphoma
- IV rituximab administration is challenging in limited resource settings, precluding widespread use
- Trial of subcutaneous rituximab (PIs: Henry Ddungu, Manoj Menon) at the UCI – started October 2019

Empiric management of infections is complicated by emerging antimicrobial resistance and changing local epidemiology of organisms.

Routine blood cultures historically not available at UCI.

Ph.D. Study Aim: To identify bacterial causes of neutropenic fever among inpatients with hematologic malignancies.

Enrolled: Ped & Adult Inpatients with heme malignancies

N=629

Cases with febrile neutropenic episode (FNE)

N=159 (25%)

Positive blood culture

N=48 (30%)
Antimicrobial-resistant gram-negative bacteria are a common cause of neutropenic fever at the UCI

**Gram-negative isolates**

- ESBL: 53 (64%)
- CRE: 19 (23%)

**Gram-positive isolates**

- VRE: 8 (62%)
- MRSA: 3 (60%)
Bacteremia is associated with poor survival outcomes

Mortality Outcomes

7 days: HR (95% CI)- 3.63 (1.49, 8.86)
30 days: HR (95% CI)- 2.17 (1.09, 4.32)
The vast majority of human genetic diversity is found in Africa

“A global reference for human genetic variation”
The 1000 Genomes Project Consortium
doi: 10.1038/nature15393
East African Adult Hematology-Oncology Fellowship Program

- Supported by the African Development Bank (ADB) through a grant to the UCI to establish an East African Oncology Center of Excellence
- Co-directors: Drs. Abrahams Omoding (UCI) and John Harlan (Univ. of Washington)
- Objectives: train physicians who will:
  - Provide high quality clinical care
  - Guide lower-level health workers
  - Conduct research in adult hematology-oncology
  - Serve as mentors to the next generation of hematologists and oncologists
- Launched May 2018; first class of 4 fellows graduated August 2020; second class of 3 fellows matriculated November 2020
Training continues to be a major Hutch activity at the UCI - FHCC

- Multiple NIH-funded training grants over past decade; current U54 and D43
- Recently awarded a new 5-year, $2 million D43 award
- Pending D43 focused on cancer genomics and genomic data science – *impact score 17*
- 5 PhD trainees currently supported; 14 long-term trainees in the field of HIVAM research
- Candidate retention in first two D43 award periods has been excellent
- Since its inception >300 individuals have taken part in at least one component of training from the UCI – FH Collaboration
- Established a Peer-Mentoring Career Development program at UCI to support ongoing research training and development of Ugandan investigators and to serve as pipeline for new trainees (Phipps *et al.*, *Journal of Global Oncology*, 2018)
- Over 100 publications have been authored or co-authored by trainees to date
- 6 trainees have received independent research awards
- Trainees are all well-positioned to pursue independent research funding through mechanisms such as the NIH K43 award, which is a 1° focus of the active D43 award
Oncology Nursing Training Program

- Co-led by Dr. Kathleen Shannon Dorcy and Arlyce Coumar of Fred Hutch/UW/Seattle Cancer Care Alliance and Sisters Allen Naamala and Agnes Agawa of UCI
- Training on lymphoma, chemotherapy complications, sepsis, hazardous drug handling delivered to >80% of UCI nursing staff over 6 visits to Uganda
- Hosted UCI nurse leaders in Seattle to Design a Uganda Cancer Institute Curriculum for Oncology Nurse Competency
- Collaborating with Hutch / UCI physicians on sepsis prevention initiative: Attendant & Care Giver Temperature Surveillance (ACTS)
SARS-CoV-2 pandemic is tracing a unique trajectory in Africa

covid19.who.int
SARS-CoV-2 PCR testing at the UCI – Fred Hutch Cancer Centre
SARS-CoV-2 vaccination in Africa: the challenging road ahead

COVID-19 vaccine doses administered per 100 people
Total number of doses administered, divided by the total population of the country.

Share of people who received at least one dose of COVID-19 vaccine
Total number of people who received at least one vaccine dose, divided by the total population of the country.

Source: ourworldindata.org
Nearly a third of Uganda’s students may never return to school.
Summary

- Cancer incidence in sub-Saharan Africa will increase steadily and significantly over the balance of the 21st century
- Existing resources — human and material — for cancer prevention, diagnosis, treatment, palliation, and survivorship in sub-Saharan Africa are inadequate to meet the current need
- Investment now in capacity building for the growing cancer burden is urgently needed to meet the current and future challenges
- The Fred Hutch has made a long-term commitment to help build capacity to meet the future cancer burden in SSA, and is looking for partners in this mission
“We are going to teach you to be rebels. Not with guns and daggers, but with science and technology.”
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THANK YOU
Join us on January 18, 2022

Topic to be announced soon!