PROPOSAL

Causes & Prevention of Stomach Cancer among Himalayan People in Nepal

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Summary

We propose to establish the causal factors for gastric (stomach) cancer in a population for which the incidence and mortality of this disease is remarkably high. An outstanding scientific team has been assembled to collaborate in the proposed research. Gastric cancer is an infection-induced, inflammation driven malignancy. Preventing or eradicating chronic infection with *Heliobacter pylori* will reduce significantly the prevalence of gastric cancer in Nepal. We will use genetic approaches pioneered in our laboratory to develop biomarkers that identify individuals at high risk of developing gastric cancer. We will characterize yet unknown environmental chemicals involved in the etiology of this devastating disease. In so doing, we address an urgent public health problem for a vulnerable population in a resource-limited setting.

Goals and Specific Aims

The overarching goal of this public health research initiative is to reduce significantly the incidence of gastric cancer among residents of rural Nepal. In approaching this ambitious but eminently achievable objective, we will pursue the following specific aims:

1. to explore systematically the risk factors for *Helicobacter pylori* infection and gastric cancer in the Sherpa and Himalayan populations in Nepal.
2. to establish strategies for treating *H. pylori* infection based on patterns of recurrence and antibiotic resistance.
3. to develop novel genetic markers that predict risk of gastric cancer in individuals with peptic ulcer disease and other precancerous lesions, facilitating early detection and potential cure.

Background

Global Epidemiology of Gastric Cancer:

Gastric (stomach) cancer is the 3rd leading cause of cancer death globally, with one million new cases reported in 2018.[1] Asia bears nearly 50% of the global burden from this disease.[1] Survival rates for stomach cancer are generally poor. Survival is higher in Japan and South Korea (50-60%) where systematic screening facilitates early detection and surgical treatment of tumors.

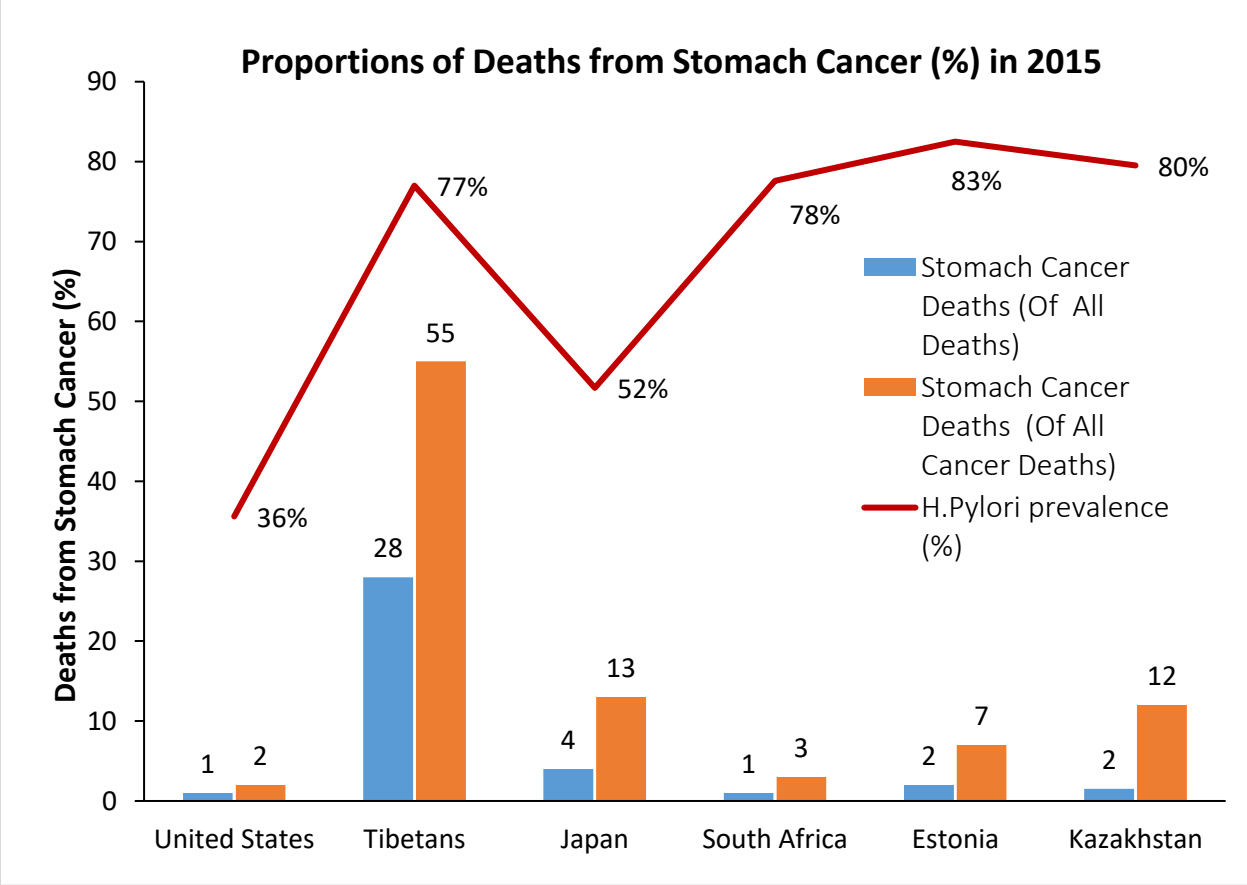
The strongest risk factor for stomach cancer identified to date is chronic infection with the bacterium Helicobacter pylori.[3] The age at which the *H. pylori* infection is acquired modulates risk since infection in high-risk areas is usually acquired in childhood. Cancers occur more frequently in regions where childhood infection is common. *H. pylori* infection alone does not result in gastric cancer. Rather, it appears that interactions between *H. pylori*, environmental carcinogens, and genetic risk factors initiate molecular changes that cause this devastating disease.

Gastric Cancer in rural Nepal:

In Nepal, among males, gastric cancer is the 2nd most common cancer, after cancer of the lung.[2] People of Tibeto-Burman origin, i.e., Sherpas, Tibetans, Tamang and Gurung are singularly affected. In Kathmandu, Nepal, 45% of all patients with gastric cancer admitted for surgery were of Tibeto-Burman origin, a disproportionate disease burden given that this population constituted only 18% of the Nepalese population.[3]

At the Kunde Hillary Hospital – built by Sir Edmond Hillary, an exceptionally high mortality rate for stomach cancer (136/100,000 per annum) was reported for the Sherpa population[4] while the global mortality rate for this disease is 8/100,000 per annum. The incidence/mortality rate among Sherpas in the 1990's is significantly higher than that observed in Japan and Korea after World War II (60-90/100,000), which, at the time, were the highest in the world. The *H. pylori* infection prevalence observed for the Sherpa population in Khumbu, Nepal is 70% with a prevalence of 78% in Sherpa children <10 years of age.[4] And for Tibetans residing in Dharamsala, India, gastric cancer is the leading cause of death, accounting for nearly one-third of all deaths recorded in the Delek Hospital between 2015-2017 (Figure 1).

Figure 1.



Data source: World Health Organization cancer mortality statistics, Death record of Tibetan Delek Hospital, Dharamsala, and Hooi JKY et al. Gastroenterology, 2017

Dietary Factors and Risk of Gastric Cancer:
Landmark studies in Japan revealed that high salt consumption and salted food are important risk factors for gastric cancer, as is the use of food preservatives containing nitrites.[5-7] Moreover, a body of literature suggests that salt can synergize with *H. pylori* infection in causing gastric cancer.[8]

Sherpas and other peoples of Himalayan origin have dietary practices associated with an increased risk of gastric cancer, including a high consumption of salted-butter tea, salted and dried meat (beef and yak), meat, and low amounts of fruits and vegetables. Moreover, Sherpas have adopted the practice of consuming bottled pickles with high salt content.

Molecular profiling of gastric cancer:
Genome sequencing studies of gastric cancer have been published (Figure 2). These studies reveal that mutational processes related to defective DNA repair pathways and aberrant expression of DNA-editing genes contribute to cancer mutations. Importantly, three mutational signatures of unknown etiology are associated with gastric cancers. One such mutation, Signature 17 in the COSMIC database of mutational signatures (Figure 2), involves A:T to C:G mutations, and is abundant in nearly half of all gastric cancers![9] Thus, by sequencing gastric cancer DNAs, obtained from high-risk populations in Nepal, we can determine if mutational signatures in Sherpas and other Himalayan populations differ from those observed elsewhere in the world.

Figure 2.

Contribution of mutational signatures in whole genome gastric cancer sequences with > 5 mutations per MB (45% of cases). Adapted from Alexandrov, et al, *Nat Comm* (2015). Original data from Wang, et al, *Nat Genet*. (2014).

Significance

This molecular epidemiologic research is designed to establish causal factors for gastric cancer, providing leads to the prevention and management of this uniformly fatal disease. Guidelines are urgently needed for screening and treatment of *H. pylori* infection and for endoscopic surveillance of populations at risk. Current knowledge of drug susceptibility patterns of *H. pylori* is insufficient to guide antibiotic therapy in clinical practice. Defining environmental and genetic risk factors for gastric cancer in this study population will benefit high-risk populations in many countries in addition to those living in the Himalaya.

We chose to study a population with an exceptionally high prevalence of gastric cancer (Fig 1). Our community-based screening model and engagement of community members ensure full participation in the project. Use of a novel adductomics approach to profile genetic markers will identify individuals at high risk of developing gastric cancer. This research will inform public health practices in Nepal and can serve as a model for other translational research.

PARTICIPANTS

Investigators

This research is a collaborative project involving the Zickler Laboratory of Chemical Biology (LCB) at Stony Brook University, the Johns Hopkins University, Mount Sinai Medical Center, and a collaborating hospital/institution in Kathmandu, Nepal. Kunchok Dorjee, M.D., Ph.D. Senior Research Associate, will lead the public health and clinical components. Arthur P. Grollman, M.D., Distinguished Professor of Pharmacological Sciences and Medicine will serve as Principal Investigator, Thomas Rosenquist, Associate Professor of Pharmacological Sciences at Stony Brook University and Masaaki Moriya, Professor of Pharmacological Sciences will conduct the analytical and genetic research involved in this study. Professor Boffetta participated with Dr. Dorjee, in designing the epidemiologic component of the study.

Kunchok Dorjee, M.D. Ph.D. is a physician-epidemiologist with global health experience including extensive clinical research involving Tibetan and Sherpa populations in India and Nepal. Dr. Dorjee successfully led a population-wide initiative supported by the World Health Organization, which conducted active case-finding of tuberculosis among Tibetans. Currently he leads a tuberculosis elimination campaign for Tibetans living in India. Dr. Dorjee was awarded the prestigious Kochon prize for this work. He will assemble our study cohort consisting of Sherpas and other Himalayan origin people in Nepal.

Arthur Grollman, M.D., a physician and cancer biologist, has made many contributions to cancer research. Recently, Grollman and his team established aristolochic acid as the causative agent of upper urothelial cancer in the Balkans and in Taiwan. These seminal studies were supported by the Laufer Family Foundation, National Cancer Institute and Fogarty Foundation. Dr. Grollman is intimately familiar with the Sherpa and Himalayan communities, having served as physician on high altitude trekking expeditions throughout Nepal. His curriculum vitae and full list of publications can be accessed at https://renaissance.stonybrookmedicine.edu/lcb/grollman.pdf

Paolo Boffetta, M.D. is an internationally renowned cancer epidemiologist whose interests include environmental causes of cancer. His extensive accomplishments and involvement in international research collaborations led to the establishment of a number of cancer consortia, including one on stomach cancer (stop-project.org/), and over 1,200 scientific publications. We are very fortunate that our project has attracted Dr. Boffetta's interest and participation as a co-investigator. Please see letter on p. 17.

Thomas Rosenquist, Ph.D., a molecular geneticist, will study this gastric cancer cohort using adductomics, a novel method developed by his laboratory. In recognizing the significance of this research, NIH awarded Rosenquist an RO1 grant with a perfect priority score of 1.0, a rare distinction in NIH grant reviews!

Masaaki Moriya, Ph.D., a molecular biologist, has made numerous contributions to carcinogenesis research. His experience in characterizing environmental carcinogens will be indispensable in our efforts to identify agents involved in the etiology of gastric cancer in rural Nepal.

Collaborators

Dr. Dorjee is very well acquainted with the Sherpa community and has established working relationships with many individuals from this community including leadership at the American Himalayan Foundation. Mr. Norbu Tenzing Norgay Sherpa, son of the late Tenzing Norgay Sherpa, has expressed his support for Dr. Dorjee's commitment to improve the health of the Himalayan community. Dr. Dorjee also has relationships with Dr. Kundu Yangzom, a board member of the Nick Simons Institute, and with Mr. Tshering Dorjee Lama (Tsedo) of the American Himalayan Foundation. Mr. Lama is highly motivated to assist with this project, as several siblings died of gastric cancer.

Nick Simons Institute

Our project closely aligns with the vision of Nick Simons to improve the health of residents of rural Nepal. We are grateful to the Nick Simons Institute for encouraging this project. Dr. Dorjee appreciates the mission, core values, and priorities of the Nick Simons Institute (NSI) and has discussed this project with Dr. Anil Shrestha, Executive Director of the NSI in Kathmandu. Dr. Shrestha reviewed this proposal in which we propose to study the prevalence

and risk factors for *H. pylori* infection and gastric cancer, capture socio-demographic, dietary and other risk factors while using state-of-the-art analytical techniques to identify the causative factors of this disease.

Identifying the factors underlying the high prevalence of chronic gastritis, peptic ulcer disease, and gastric cancer will inform the dietary, behavioral and clinical practices needed to prevent gastric cancer in the rural populations in Nepal. Genomic analysis will enable early detection of this cancer, potentially achieving cures! We are aware of the extensive capacity building activities for rural health for which the NSI is responsible, and therefore, we will be careful not to create additional responsibility to the Institute. We envisage that the NSI will interact with our project as follows:

1) Facilitate identification of a collaborating partner through which we can recruit a Program Manager and nurse Program Coordinator to oversee various organizational and clinical aspects of this project ensuring smooth implementation of *H. pylori* screening and treatment, coordination of stakeholders, retrieval of gastric biopsy specimens and community education.

2) Facilitate identification of a district hospital(s) in rural Nepal where a significant population of Sherpas and Himalayan origin people currently seek medical care so that risk factors for *H. pylori* infection and gastric cancer can be conveniently studied. We understand that the district hospital may or may not be an NSI supported district hospital given the focus of our study of Himalayan origin people. We will consult the NSI leadership in locating a suitable district and district hospital for implementation.

3) Facilitate identification of a tertiary care center with facilities for upper gastrointestinal endoscopy and gastric biopsy; and a cancer treatment center where gastric biopsy specimens of newly diagnosed gastric cancer cases can be obtained.

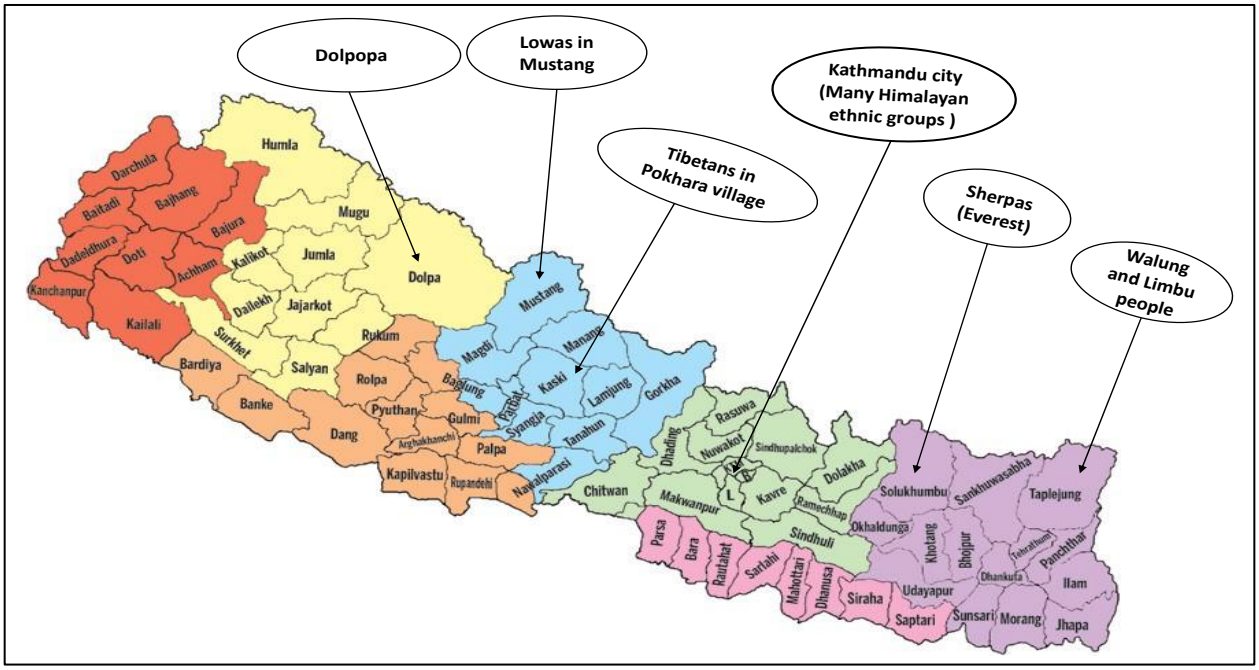
4) Facilitate coordination with Governmental agencies for possible regulatory issues.

RESEARCH PLAN

Study Population

Our study cohort consists of populations of Himalayan origin residing in Nepal (Figure 3). Our study will be based at an NSI-supported hospital. Epidemiological surveys and screening for *H. pylori* infection will take place at this hospital. To identify cases of gastric cancer, we will collaborate with physicians based at a cancer treatment center in Kathmandu. An ethnically different group such as Chhetri, Brahmin, etc. will serve as a control population. We consider the district of Solukhumbu to be the home district of the Sherpa population and will seek advice from the leadership of the NSI regarding other districts to consider for our project, and tertiary care centers where upper gastrointestinal endoscopies and gastric biopsies are routinely carried out.

Figure 3. Himalayan origin people in Nepal



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New York, April 26th, 2019

Dr. Marilyn Simons, President
Simons Foundation

Dear Dr Simons,

I enthusiastically support the proposal, "Causes and Prevention of Stomach Cancer among Himalayan Populations in Nepal," prepared by Dr. Grollman and his collaborators. Stomach cancer is a major cause of cancer incidence and mortality globally, and specifically in high-risk population such as the Sherpas in the Himalayan region. While infection with Helicobacter pylori is a major cause of the disease, it is not a sufficient one, and other, poorly known risk factors are likely to operate, and to differ between populations. The important problem of the prevention of stomach cancer in the Sherpas and other high-risk populations can be best addressed through a multi-disciplinary approach such as that proposed by Dr. Grollman.

Over the years I have extensively studied the global epidemiology and prevention of stomach cancer and its precursor lesions; I published over 35 scientific publications on this subject and have initiated the StoP Consortium, an international collaboration of over 30 centers sharing data and biological samples in global projects in the etiology, mechanism and prevention of stomach cancer (stop-project.org/).

I will provide expertise and mentoring on the epidemiologic aspects of the proposed study, including the design, conduct, analysis and interpretation of the case-control and the cross-sectional studies, and will contribute to integrate the epidemiologic and the molecular results.

Please do not hesitate to contact me further on the subject of this proposal.

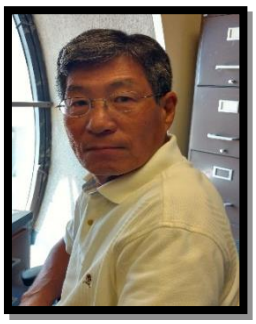
Sincerely,

Paolo Boffetta, MD, MPH
Associate Director for Global Oncology, The Tisch Cancer Institute
Icahn School of Medicine at Mount Sinai

Laboratory of Chemical Biology

Thomas Rosenquist
mouse genetics

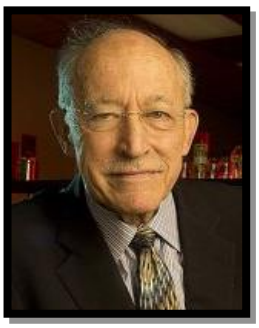
Kathleen Dickman
cell biology



Masaaki Moriya
mutational signature

Radha Bonala
chemistry

Keiji Hashimoto
molecular biology



Arthur P. Grollman
Director

Cinthia Alvarez-Buonaiuto
Asst to the Director

https://renaissance.stonybrookmedicine.edu/lcb

Research Overview

The Laboratory for Chemical Biology (LCB) was founded in 1988, assisted by a generous gift from Mr. and Mrs. Leo Zickler of Washington, D.C. Currently, the Laboratory is directed by Arthur P. Grollman M.D., Distinguished Professor of Pharmacological Sciences, Professor of Medicine and Evelyn Glick Professor of Experimental Medicine.

In the LCB, molecular and cell biologists collaborate with chemists in exploring relationships between the three-dimensional structures of damaged DNA and the function of enzymes involved in its repair. Toward that end, mechanisms of DNA damage recognition, mutational specificity, DNA replication and repair are studied at the cellular, molecular and atomic levels.

LCB investigators pioneered the development of site-specific systems used to explore mechanisms of mutagenesis induced by defined DNA lesions, and to elucidate enzymatic pathways for the repair of oxidative DNA damage in mammalian cells. Earlier research from the LCB was instrumental in establishing mechanisms by which the radiomimetic anti-tumor drug, bleomycin, generates unique strand breaks in duplex DNA. Additionally, translational research by LCB investigators linked endometrial cancer with exposure to the antiestrogen, tamoxifen.

Recently, LCB scientists brought their interdisciplinary strengths to bear on the etiology of human cancer. The unsuspected carcinogenicity of certain herbal remedies was revealed by their seminal studies of Aristolochia toxicity. This research illustrates the power of combining mechanistic information with molecular epidemiological approaches in establishing causative linkages between environmental mutagens and human disease.