TWENTY YEARS OF COLLABORATION WITH THE QIDONG LIVER CANCER INSTITUTE:THE JOHNS HOPKINS EXPERIENCE

Thomas W. Kensler, Patricia A. Egner, John D. Groopman
(Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA)

Abstract: On the occasion of the 40th anniversary of the Qidong Liver Cancer Institute (QDLCI) this report highlights two decades of collaborative research between investigators at the QDLCI and Johns Hopkins University focused on enhancing our understanding of the etiology and prevention of hepatocellular carcinoma. Successes in these endeavors have been driven by shared scientific goals, hard work and deep-rooted friendships.
Key words: liver cancer; chemoprevention; aflatoxin; Qidong

与启东肝癌防治研究所协作的 20 年:约翰霍普金斯大学的经验

托马斯·肯瑟勒,盼鹊西亚·英格纳,约翰·格鲁普曼
(约翰霍普金斯大学布隆伯格公共卫生学院环境卫生学系,美国 巴尔的摩 21205)

摘　要:值启东肝癌防治研究所建所 40 周年之际,就约翰霍普金斯大学和启东肝癌防治研究所在过去 20 年中在肝癌病因学和预防协作研究方面的共识和亮点作一报道。共同的科学目标、努力的工作以及深厚的友谊是取得成功的动力。
关键词:肝癌;化学预防;黄曲霉毒素;启东
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"Friendship is the only cement that will ever hold the world together"—Woodrow Wilson, Twenty-eight President of the United States of America

We first came to Qidong in 1993, using a Russian hydrofoil to bring us from Shanghai up the Huangpu and into the now defunct ferry docks of Qidong on the north branch of the Changjiang. We were met by Dr. Yuan-Rong Zhu, director of the Qidong Liver Cancer Insitute (QDLCI) and Dr. Bao-Chu Zhang, chief of clinical oncology. Our visit was arranged by Dr. Geng-Sun Qian, director of the Carcinogenesis Program of the Shanghai Cancer Institute and Dr. Lu-Yi Yu, of the Shanghai Medical University (Figure 1). We had met Dr. Qian years earlier when he was on sabbatical at the US Food and Drug Administration (FDA). The center of the city, Huilong, was only a few blocks of three story buildings and a dead-end dirt road led to the only open hotel, the Qidong 2nd Guest House. The transitions in Qidong in the subsequent two decades are breathtaking. The new ChongQi bridge linking Shanghai to Qidong in late 2011 will only accelerate the transformations. However, even in 1993, the QDL-

Address editorial correspondence to: Dr. Thomas W. Kensler. Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe St., Baltimore, MD 21205, USA
E-mail: tkensler@jhsph.edu
(T) 001-410-955-1292
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CI, was a dominant structure in the town, fronted by a well tended garden that is still in place today, and an internationally recognized center for research on liver cancer.

Tours of the clinic, the tumor specimen collection and cancer registry, a field trip to rural townships where mortality rates from hepatocellular carcinoma (HCC) were extraordinarily high as well as extended discussions on their research activities in screening, etiology and prevention led to an initial collaboration to monitor aflatoxin B1 (AFB1) exposures in rural residents. A reciprocal visit of the QDLCI leaders to Johns Hopkins University the following year facilitated the initial preparation and submission of joint grant applications for funding from the US National Institutes of Health for more extensive projects. This report describes the key accomplishments of the Johns Hopkins–QDLCI projects over the past two decades, with special emphasis on etiology and chemoprevention of HCC.

1 ETIOLOGY OF LIVER CANCER

1.1 Aflatoxin Biomarkers

A strong case for the importance of chemical and viral factors in the etiology of liver cancer emerged from a cohort study incorporating hepatitis B virus and aflatoxin biomarkers. This study, comprising more than 18 000 men in Shanghai, examined the interaction of hepatitis B virus (HBV) and aflatoxin biomarkers as independent and interactive risk factors for HCC. The nested case-control data revealed a statistically significant increase in the relative risk of 3.4 for those HCC cases in whom a urinary aflatoxin biomarker was detected. For men whose serum was HBsAg positive but whose urine did not indicate aflatoxin exposure, the relative risk was 7, and in individuals exhibiting both urinary aflatoxin marker and positive HBsAg status, the relative risk was 59[1,2]. These measures were conducted on single urine and serum samples from each individual in the cohort, respectively.

left to right: Drs. Yu, Groopman, Kensler, Davidson, Zhu, Qian and Zhang

Figure 1 During our first visit to the QDLCI in September 1993

Our initial Johns Hopkins–QDLCI collaboration consisted of a longitudinal study designed to measure aflatoxin biomarkers in residents of Daxin Township, Qidong[3]. Serial measures of levels of aflatoxin adducts with albumin was examined in two periods: September-December 1993 (wave 1) and June-September 1994 (wave 2). During the 12-week monitoring period of wave 1, 120 individuals provided multiple blood samples. AFB1-albumin adducts were detected in all but one of these 792 serum samples. Using linear regression models on the samples collected weekly during each wave, the mean aflatoxin-albumin adduct levels increased ($P<0.05$) during the 12 weeks of wave 1 and decreased ($P<0.05$) over the 4 months of wave 2. Neither HBV surface antigen status nor gender modified either the baseline mean or the temporal trend. These data defined the prevalence and temporal patterns of aflatoxin exposure in Qidong.

This sample set also provided opportunities for development and validation of analytical [4,5] and statistical methods[6]. For example, urine samples from early collections were used to optimize isotope-dilution mass spectrometry methods for measuring aflatoxin-DNA adduct biomarkers and other metabolites[4]. These newer analytical methods provided improved sensitivity and specificity to measure ambient levels of exposures in participants of the intervention studies described *infra*.

To examine the consequences of aflatoxin exposure on mutagenesis–an important component of carcinogenesis, we determined somatic mutation frequency in the human hypoxanthine guanine phosphoribosyl transferase gene (HPRT). Ninety healthy subjects from Daxin were assigned as low or high exposure to AFB1 according to a dichotomization around the population mean of their levels of aflatoxin-albumin adducts. HPRT mutant frequency was determined in individuals by a T cell clonal assay. An odds ratio(OR) of 19.3 (95%CI: 2.0~183) was demonstrated for a high HPRT mutation frequency in individuals with high aflatoxin exposure compared with those with low aflatoxin exposure. While this cross-sectional study suggested the potential use of mutation frequency of the HPRT gene as a long-term biomarker of aflatoxin exposure, the logistical and regulatory challenges associated with shipping fresh, viable lymphocytes to overseas labs expert in the assay has precluded its expanded use[7].

1.2 Aflatoxin and *p53* Mutations

The relationship between aflatoxin exposure, mutation and development of HCC has been further highlighted by molecular biological studies on *p53*, a tumor suppressor gene commonly mutated in many human cancers[8]. Two simultaneously published studies showed the first linkage between aflatoxin exposure and a specific mutation in *p53*, one based upon Qidong samples[9]. Subsequently, many studies of *p53* mutations in HCC in populations exposed to high levels of dietary aflatoxin have found high frequencies of G:C to T:A transversions, with clustering at codon 249[10]. In contrast, no mutations in codon 249 were found in *p53* in HCC from Japan and other areas where there was little exposure to aflatoxin. Initially, we evaluated genetic alterations in 24 liver resection specimens from Shanghai and Qidong. HBV was integrated in all patient samples. Alterations of *p53* were present in 95% of the cases. All seven HCCs with a *p53* mutation from Qidong and three of five from Shanghai had the aflatoxin-associated point mutation with a G to T transversion at codon 249[11].

Studies by others in Qidong revealed that HBV hepatitis is ubiquitous in Qidong HCC cases, whereas hepatitis C virus contributes little to its risk. They observed that even modest levels of aflatoxin exposure tripled the risk of HCC in HBV-infected men[12,13]. In a seminal study[14] reported detection of *p53* codon 249 mutations in plasma of liver tumor patients residing in The Gambia, however, the mutational status of their tumors was not determined. In a follow-up study utilizing a Qidong cohort, we compared results in plasma DNA with sequencing of DNA for specific *p53* mutations from 25 HCC tumors[15]. Mutations were detected in 10 samples. Analysis of 20 additional plasma-tumor pairs showed that 11 tumors and 6 plasma sam-

ples contained the specific mutation. Ten plasma samples from healthy individuals were all negative. We developed an electrospray ionization mass spectrometry(ESI-MS)-based method called short oligonucleotide mass analysis(SOMA) for these mutation analyses. This SOMA method exhibited greater sensitivity compared to the standard molecular biology assay using mutation detection by RFLP[16].

Jackson, *et al.*[17] further explored the temporality of detection of this mutation in plasma before and after clinical diagnosis of HCC in the same patient. This study was facilitated by availability of a longitudinal collection of plasma samples from a cohort of 1 638 high-risk individuals in Qidong, who continue to be followed since 1992. Sixteen patients diagnosed with liver cancer between 1997 and 2001 from which plasma samples collected before and after HCC diagnosis were selected for study. In samples collected prior to liver cancer diagnosis, 22% of the plasma samples had detectable levels of the codon 249 mutation in *p53*. The persistence of this pre-diagnosis marker was borderline statistically significant. The codon 249 mutation was detected in 45% of all plasma samples following the diagnosis of HCC. This level of positive samples following liver cancer diagnosis compares with about 50% of all liver tumors in Qidong, suggesting a nearly 90% concordance between plasma and tumor *p53* codon 249 mutation outcome. Further, persistence of this mutation in plasma once it became measurable was statistically significant in repetitive samples following diagnosis. Nearly one-half of the patients were positive for this marker at least 1 year and in one case 5 years prior to diagnosis of HCC.

1.3 HBV Mutations and HCC

The contribution of HBV to the pathogenesis of liver cancer is multifactorial and is further complicated by the identification of mutant variants in HBV that may alter their contributions to the carcinogenic process. In many cases of HCC in Asia and Africa, a double mutation in the HBV genome, an adenine to thymine transversion at nucleotide 1762 and a guanine to adenine transition at nucleotide 1764 (1762^{T}/1764^{A}), has been found in tumors. A recent meta-analysis examined the relation of a number of mutations in HBV to the risk of HCC and found that the qualitative presence of the HBV 1762^{T}/1764^{A} mutation bestowed a significant increased odds of HCC(OR=3.79, 95%CI: 2.71~5.29)[18].

In several studies in Qidong, we have found that the HBV double 1762^{T}/1764^{A} mutation was not only detectable in plasma samples at the time of HCC diagnosis, but could be measured in some individuals up to 15 years prior to diagnosis[19~21]. Most recently, we have utilized real-time PCR to quantitatively measure levels of the HBV double 1762^{T}/1764^{A} mutation in plasma samples from a matched case-control investigation of 345 men who died of HCC and 625 controls who were nested within a cohort of male HBsAg carriers[21]. Matched preserving OR were used as a measure of association and 95% confidence CI as a measure of precision. A total of 278 (81%) of the cases were positive for the HBV 1762^{T}/1764^{A} mutation compared to 250(40%) of the controls. The matched preserving OR of 6.72(95%CI: 4.66~9.68) strongly indicated that cases were significantly more likely than controls to have the mutation. Plasma level of DNA harboring the HBV mutation were on average 15-fold higher in cases compared to controls. Thus, within this cohort of HBsAg carriers at high risk of developing HCC, individuals positive for the HBV 1762^{T}/1764^{A} mutation at enrollment were substantially more likely to subsequently develop HCC, with a higher concentration of the mutation in plasma enhancing predisposition for cancer development.

As part of this program, Tu and colleagues[22] have also compared the complete sequence of HBV isolated from 20 HCC and 35 non-HCC patients in Qidong. These results implicate A2189C and G2203W as new predictive markers for HCC. The OR were 3.99 (95%CI: 1.61~9.92) and 9.70 (95%CI: 1.17~80.58), respectively, for A2189C and G2203W. A separate longitudinal study demonstrated that six point mutations,

including T1653, V1753, T1762, A1764, T1766 and A1768 were found to occur more frequently in HCC than non-HCC patients. T1653 and V1753 were risk factors independent of the double mutation for HCC[23].

1.4 Impact

Much has been learned about the etiology of HCC from studies conducted in Qidong, especially those that utilize their extensive and comprehensive longitudinal cohorts of high-risk individuals. Identification of key risk factors prompts approaches to their elimination as well as yielding improved tools for screening for individuals at highest risk of developing HCC. As with all cancers, one effective means for reducing morbidity and mortality is earlier diagnosis. For HCC, the current modalities for screening, such as monitoring for serum alpha-fetoprotein or imaging, are not especially predictive or cost effective, respectively. There are unmet needs to use our expanding understanding of the underlying mechanistic bases for HCC development to develop high-throughput, inexpensive, predictive molecular probes as screening tools. The identification of mutations in *p53* as well as the HBV genome that reflect key risks for HCC offers several possibilities. Continued efforts to validate and apply these tools for earlier diagnosis of HCC are needed.

2 CANCER CHEMOPREVENTION

Cancer chemoprevention is a key strategy for the secondary prevention of cancer. This approach entails the use of drugs, dietary supplements or functional foods to retard, block or even reverse the carcinogenic process. These strategies serve to alter cell fate, by either preventing cells from acquiring genetic damage or by impeding the proliferation of preneoplastic cells or, alternatively, accelerating their apoptosis. One successful strategy for cancer chemoprevention is modulation of hepatic metabolizing enzymes, leading to a facilitated elimination of endogenous and environmental carcinogens. Inducers of carcinogen-conjugating enzymes such as glutathione transferases by dithiolethiones and sulforaphane inhibit tumorigenesis of environmental carcinogens in various animal models [24,25].

2.1 Chlorophyllin

The anticarcinogenic properties of chlorophyllin, a water-soluble, over-the-counter derivative of chlorophyll, have been demonstrated in a number of animal models, including prevention of AFB1-induced HCC[26,27]. Although the primary mode of action is thought to be the sequestration of aflatoxin by chlorophyllin in the gastrointestinal tract—thereby impeding absorption, we have characterized enzyme-inducing properties that may also contribute to its mechanism of action[28]. In a randomized, double-blind, placebo-controlled chemoprevention trial conducted in Qidong in 1997, chlorophyllin was determined to alter the disposition of aflatoxin[29,30](Table 1). One hundred and eighty healthy adults were randomly assigned to ingest 100mg of chlorophyllin or a placebo three times a day prior to each meal for 4 months. The primary endpoint was modulation of levels of urinary aflatoxin-N^7-guanine adducts collected three months into the intervention. Adherence to the study protocol was outstanding, and no adverse events were reported. Aflatoxin-N^7-guanine could be detected in 105 of 169 available samples. Chlorophyllin consumption at each meal led to an overall 55% reduction in median urinary levels of this aflatoxin biomarker compared with those subjects taking placebo. A recent small Phase 0 study by Jubert, *et al.*[34] using accelerator mass spectrometry to investigate the absorption and pharmacokinetics of doses of [^{14}C]AFB1 indicated that interventions with chlorophyllin reduced AFB1 uptake and distribution among all subjects. These results affirm that chlorophyllin mediates reductions in systemic uptake of aflatoxin in humans, as seen in preclinical models and surmised from the clinical trial in Qidong.

2.2 Oltipraz

1,2-Dithiole-3-thiones were reported in the 1950s to be constituents of cruciferous vegetables in Czechoslovakia[35]. Oltipraz, a substituted 1, 2-dithiole-3-thione, was originally developed by the pharmaceutical industry as a possible treatment for schistosomiasis

Table 1 Summary of randomized clinical intervention trials in Qidong

Agent	Dose and Schedule	Size (duration)	Biomarker Modulation	References
Oltipraz	●Placebo, q.d. ●125mg, q.d. ●500mg, q.d.	234 (2 months)	2.6-Fold increase in urinary excretion of AFB-NAC at 1 mo. (125mg) and 51% decrease in AFM1 at 1 mo. (500 mg); 6% decrease in AFB-AA at 2 mo. (500 mg); no effect on urinary mutagens or oxidative DNA damage products	Jacobson, *et al.* (1997), Zhang, *et al.* (1997)[31], Kensler, *et al.* (1998)[40], Wang, *et al.* (1999)[41], Camoirano, *et al.* (2001)[32], Glintborg, *et al.* (2006)[33]
Chlorophyllin	●Placebo, q.d. ×3 ●100mg, q.d. ×3	180 (4 months)	55% decrease in urinary excretion of AFB-N^7-Gua DNA adducts at 3 mo.	Egner, *et al.* (2000, 2001)[29,30]
Broccoli Sprout GRR	●Placebo, q.d. ●400μmol GRR	200 (14 days)	9% decrease in urinary excretion of AFB-N^7-gua DNA adducts at 10 days; 10% decrease in pollutant PheT excretion	Kensler, *et al.* (2005)[47]
Broccoli Sprout GRR↔SFR Cross-over	●Run-in→GRR(800μmol)→wash-out→SFR(150μmol) ●Run-in→SFR→wash-out→GRR	50 (24 days)	Glucoraphanin and sulforaphane elimination pharmacokinetics; 20%~50% increases in urinary excretion of mercapturic acid (NAC) conjugates of air pollutants: acrolein, ethylene oxide, crotonaldehyde, benzene	Egner, *et al.*(2011)[48], Kensler, *et al.* (2012)[49]
Broccoli Sprout GRR + SFR Blend	●Placebo ●GRR(600μmol) +SFR (40μmol)	291 (12 weeks)	In progress: primary endpoints are urinary biomarkers of food- and air-borne toxins and pollutants	unpublished

and was extensively evaluated in clinical trials in the early 1980s. While studying mechanisms of antischistosomiasis by oltipraz, Bueding and colleagues at Hopkins initially noted that giving the drug to mice markedly elevated glutathione levels in many tissues[36] as well as enzymes important to carcinogen detoxication in multiple tissues[37,38]. These results prompted Bueding to predict that oltipraz might have cancer chemopreventive properties. This prediction held true, as upon extensive preclinical evaluation by the National Cancer Institute and others, oltipraz was found to be effective as an anticarcinogen in nearly a score of animal models[39].

Aflatoxin biomarkers were used as intermediate endpoints in a Phase Ⅱa chemoprevention trial of oltipraz conducted in Daxin, Qidong in 1995[40,41]. This was a placebo-controlled, double-blind study in which participants were randomized to receive placebo or 125mg oltipraz daily or 500mg oltipraz weekly. Urinary aflatoxin M1 levels were reduced by 51% compared with the placebo group in persons receiving the 500mg weekly dose. No significant differences were seen in urinary aflatoxin M1 levels in the 125mg group compared with placebo. This effect was thought to be due to inhibition of cytochrome P450 1A2 activity. Median levels of aflatoxin-mercapturic acid (a glutathione conjugate derivative) were elevated 2.6-fold in the 125mg group, but were unchanged in the 500mg group. Increased aflatoxin-mercapturic acid reflects induction of aflatoxin conjugation through the actions of glutathione transferases. The apparent lack of induction in the 500mg group probably reflects masking caused by diminished aflatoxin-8, 9-epoxide formation for conjugation through the inhibition of CYP1A2 seen in this group. This initial study demonstrated for the first time that aflatoxin biomarkers could be modulated in humans in a manner that would predict decreased disease risk.

2.3 Sulforaphane

Although the initial oltipraz clinical trial demon-

strated the proof of principle for increasing pathways leading to aflatoxin detoxication in humans, the practicality of using a drug-based method for prevention in the economically developing world is limited where approaches to "frugal medicine" are needed[42]. Many foods have high levels of enzyme inducers[43,44]. A beverage formed from hot water infusions of 3-day old broccoli sprouts, containing defined concentrations of glucosinolates as a stable precursor of the anticarcinogen sulforaphane, was evaluated for its ability to alter the disposition of aflatoxin in a clinical trial conducted in HeZuo, Qidong in 2003. Sulforaphane has been extensively examined for its chemopreventive properties in animals[45,46]. Two hundred healthy adults drank beverages containing either 400 or <3μmol glucoraphanin nightly for 2 weeks. Urinary levels of aflatoxin-*N*7-guanine were slightly lower in the glucoraphanin-rich intervention arms. However, measurement of urinary levels of sulforaphane metabolites indicated striking inter-individual differences in bioavailability. This outcome may reflect individual differences in the rates of hydrolysis of glucoraphanin to sulforaphane by the intestinal microflora of the study participants. Accounting for this variability, a significant inverse association was observed for excretion of total sulforaphane metabolites and aflatoxin-*N*7-guanine adducts in individuals receiving broccoli sprout glucosinolates[47]. Those individuals exhibiting good bioavailability of sulforaphane had lower levels of aflatoxin biomarkers. This preliminary study illustrated the potential use of an inexpensive, easily implemented, food-based method for secondary prevention in a population at high risk for aflatoxin exposures.

One of several challenges in design of clinical chemoprevention trials is the selection of the dose, formulation, and dose schedule of the intervention agent. Therefore, a cross-over clinical trial was undertaken in HeZuo, Qidong in 2009 to compare the bioavailability and tolerability of sulforaphane from two broccoli sprout-derived beverages: one was glucoraphanin-rich (GRR) and the other was sulforaphane-rich(SFR). Sulforaphane was generated from glucoraphanin contained in the GRR beverage by gut microflora or formed by treatment of GRR with myrosinase from daikon sprouts to generate the SFR beverage[48]. Fifty healthy, eligible participants were randomized into two treatment arms. The study design was as follows: 5-day run-in period, 7-day administration of beverages, 5-day washout period, and 7-day administration of the opposite intervention. Isotope dilution mass spectrometry was used to measure levels of glucoraphanin, sulforaphane, and sulforaphane thiol conjugates in urine samples collected daily throughout the study. Bioavailability, as measured by urinary excretion of sulforaphane and its metabolites, was substantially greater with the SFR (mean 70%) than with GRR (mean 5%) beverages. Inter-individual variability in excretion was considerably lower with SFR than with GRR beverage. Elimination rates were considerably slower with GRR, allowing for achievement of steady-state dosing as opposed to bolus dosing with SFR. An emerging problem in this region of China is air pollution. Therefore, urinary excretion of the mercapturic acids of the air-borne toxins acrolein, crotonaldehyde, ethylene oxide and benzene were also measured in urine samples from both pre- and post-interventions using liquid chromatography tandem mass spectrometry. Statistically significant increases of 20%~50% in the levels of excretion of glutathione-derived conjugates of acrolein, crotonaldehyde and benzene were seen in individuals receiving SFR, GRR or both compared with their pre-intervention baseline values. No significant differences were seen between the effects of SFR versus GRR. Thus, intervention with broccoli sprout-derived beverages may enhance detoxication of airborne pollutants and attenuate their associated health risks[49]. Follow-up studies with market stage broccoli, which is now a significant cash crop in Qidong, may point to a simple means for risk reduction.

Optimal dosing formulations of beverages in future studies could consider blends of sulforaphane and glucoraphanin as SFR and GRR mixtures to achieve

peak concentrations for activation of some targets and prolonged inhibition of others implicated in the protective actions of sulforaphane. With that view in mind, a placebo-controlled intervention in approximately 300 participants with a blend of 40μmol SFR and 600μmol GRR was undertaken in HeHe Qidong during 2011~2012. This study is assessing the impact of the broccoli sprout beverage on biomarkers of air pollution, and in particular, evaluating the sustainability of the intervention over several months in terms of tolerability and efficacy.

2.4 Impact

Collectively, this series of clinical trials has defined a paradigm for using biomarkers of exposures to environmental carcinogens as intermediate endpoints in the evaluation of practical and affordable interventions with strong prospects for disease reduction. Other scientists in other countries and risk settings now use this general paradigm. Further, our prevention trials with whole foods or simple extracts offer prospects for reducing an expanding global burden of cancer effectively, and, in contrast to promising isolated phytochemicals or pharmaceuticals, frugally. The studies with broccoli sprouts for example have provided a proof-of-principle that food-centered approaches for prevention may be effective and sustainable in underserved populations[42]. A recent study with the use of lyophilized strawberries for the prevention of esophageal dysplasia in China is but one extension of this view[50].

3 THE ESSENCE OF INTERNATIONAL COLLABORATIONS

There are several key elements for developing productive international collaborations that we have learned during our longstanding QDLCI–Johns Hopkins partnership. First and foremost is identifying the right people and making a commitment to the development and nurture of partnerships. There must be a genuine, bi-directional interest in building friendships and cultural understandings. Trans-national investigators should provide complementary sets of skills and resources to the projects, so that clear collaborative roles are evident to all. Diligence in maintaining regular channels for communicating and meetings are also important. The Johns Hopkins investigators have collectively spent nearly a decade of cumulative time "on the ground" in Qidong during the course of the development, conduct and renewal of our collaborative studies. Multiple reciprocal visits of Qidong scientists, clinicians, public health leaders and government leaders to Johns Hopkins have further nurtured the learning experiences and facilitated the timely conduct of the science.

Regulations at home and abroad govern the design and conduct of these collaborations. Meshing of regulatory and cultural distinctions between the collaborating countries can be challenging; this has certainly been true for our Sino-US projects where the barriers have been bilateral. International partnerships in translational research always take much longer than anticipated. Passion and commitment to achieve the goal, along with patience, are essential prerequisites. Getting regulatory, infrastructure and implementation factors synchronized is always underestimated in terms of scope and time. When international collaborative research works, the joy of new relationships, of building capacity, of making a difference in a place that has great needs, and of doing good science provides enormous satisfaction. The friendships that arise are enduring. This facet of collaboration is ever so evident in Qidong.

4 PREDICTIONS FOR THE FUTURE

The identification of geographically delineated, high-risk cohorts such as those in the HCC "hotspot" of Qidong or the esophageal "hotspot" of Linxian have provided profound opportunities to understand the underlying etiologies of these cancers and to develop and implement effective programs for their prevention, through screening and interventions. Tremendous

knowledge has been gained about HCC through the efforts of the QDLCI since its founding 40 years ago–much of it beyond the accomplishments of the Johns Hopkins–QDLCI program. For certain, the pronounced economic development in the region together with better and broader access to health care for screening and treatment, coupled with primary prevention such as vaccination, is already leading to a reduction in the burden of HCC in the younger residents of the Qidong region. While the task at present is far from completed, a future largely devoid of HCC in this area is imaginable as the primary risk factors for HCC in Qidong–HBV and AFB1–are controlled or eliminated. Lessons learned here will have to continue to be applied to other HCC "hotspots" where change is not so evident. However, an overall aging population together with adoption of life-style factors such as smoking, obesogenic diets, more sedentary lifestyles and the environmental degradation manifest as air and water pollution that often accompanies economic development is escalating the burden of cancer in China, and indeed around the world. As a result, the aggregate cancer burden may double or triple in this region over the next generation–but in different forms such as lung, breast and colon cancers, which are the hallmarks of the economically developed world. The QDLCI must be prepared to chart these changes, to understand them and to provide opportunities to blunt their impact while continuing to diminish the impact of HCC on the Qidongese.

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Top, left to right: Paul Talalay, Huang Wei-Xin, Chen Wei, Xue Xue-Feng, Chen Yong-Sheng, Jed Fahey; Zhu Jian, Sun Yan, Alvaro Muñoz, Zhang Yong-Hui, Gu Rui-Xin, Lu Jian-Hua, Kevin Kensler, Wu Yan, Thomas Kensler, Vice-Premier Zhang De-Jiang, Wang Jin-Bing, Patricia Egner; John Groopman, Chen Jian-Guo, Chen Tao-Yang, Zhu Yuan-Rong, Qian Geng-Sun, Lisa Jacobson; Mary Gorman, Huang Yi-Zhong, Wang Mo-Rong, Zhang Bao-Chu, Yu Lu-Yi, Zhang Qi-Nan; Derek Ng, Gao Ping, Xu Yong-Fei, Lu Jian-Guo, Nancy Davidson, Stephen Gange.

Figure 2 Past and present members of the QDLCI–JHU Study Team sharing the 2011 National Friendship Award

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作者简介

托马斯·肯瑟勒(Thomas Wells Kensler, Ph.D.),美国约翰霍普金斯大学布隆伯格公共卫生学院、美国匹兹堡大学教授。自1993年首次访问启东开始的20年中,60多次到启东现场开展肝癌的化学预防研究,先后从事奥替普拉(Oltipraz)、叶绿酸(Chlorophyllin)和西兰花苗茶(Broccoli sprouts tea)控制黄曲霉毒素暴露的化学预防研究等科研协作课题。1998年被南京医科大学聘为客座教授,2000年被启东肝癌防治研究所聘为荣誉教授。2007年被美国癌症研究协会授予美国癌症流行病学和预防研究杰出贡献奖 (2007 AACR–American Cancer Society Award for Research Excellence in Cancer Epidemiology and Prevention),2009年获约翰霍普金斯大学公共卫生学杰出教学金苹果奖 (2009 Golden Apple Award for Excellence in Teaching in Public Health Studies, Johns Hopkins University)。2010年,获江苏省人民政府颁发的"江苏友谊奖"。2011年,获中华人民共和国国务院颁发的"国家友谊奖"(2011 National Friendship Award, PRC)。

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