E Hō mai ka ʻIke Kupuna no ke Ola: Links between Traditional Native Hawaiian Concepts of Health and Epigenetic Research

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Inherent in the traditional Native Hawaiian concept of health is the understanding that environmental factors, including nutrition and social behaviors, *trans*-generationally impact health outcomes in individuals and communities. Epigenetic mechanisms may now explain molecular links between these environmental factors and health outcomes. This article explores the epigenetic concepts present in ancestral Hawaiian wisdom of health as well as an example that this knowledge inspired further biological insight into the anticancer activities of noni (*Morinda citrifolia*). Noni is one of many medicinal plants that have been utilized for centuries by Native Hawaiian health practitioners, kāhuna lāʻau lapaʻau, to address various health ailments, including cancer. Here, we report a link between the anticancer effects of noni and epigenetic gene regulation, suggesting that the traditional Native Hawaiian concept of health likely included a mechanistic rationale for the role of the environment on physical health and wellness.

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The Concept of ʻĀina in Hawaiian Culture and Health

Pūʻali kalo i ka wai ʻole," meaning "Taro, for lack of water, grows misshapen," is a Hawaiian proverb suggesting that lack of caring for the land leads to illness (Pukui, 1983, p. 296). This proverb expresses a fundamental idea present in the traditional Native Hawaiian perspective of health, which is compatible with a modern concept of a relatively "new" field of biomedical science known as epigenetics. Epigenetics is the study of heritable changes in phenotype not due to changes in DNA sequence. Epigenetic processes respond to environmental stimuli that occur as part of healthy development; however, alterations to normal epigenetic processes can lead to disease conditions such as cancer (Hong et al., 2005; Maunakea, Chepelev, & Zhao, 2010). Although the field of epigenetics is considered relatively new to biology, the underlying concept that the environment may influence health *trans*-generationally is not. For centuries, Native Hawaiians understood that an individual's physical environment, which included but was not limited to one's own exposures to certain behaviors, stress, and nutrition—as well as that experienced by prior generations—plays an essential role in the health of that individual and that of future generations. In addition to understanding such concepts, ancient Hawaiians implemented this in their daily lives. An example of this is in their knowledge of medicinal plants and healing practices.

The relationship between ancient Hawaiians and the ʻāina (land) that encompassed their physical environment contrasts with the Western perspective of land as a commodity of ownership. In fact, the Hawaiian perspective of land includes a subservient attitude of respect, as exemplified by the saying, "He aliʻi ka ʻāina; he kauwā ke kanaka," meaning "The land is a chief, man is its servant" (Pukui, 1983, p. 62). This respect for the land as a higher "rank" than man also served as a focal point for Hawaiian spirituality. Before Western contact, much of the plants, animals, and topography that shaped the physical environment of ancient Hawaiians served as manifestations of Hawaiian gods, demigods, ancestors, and family guardians known as ʻaumākua, all of whom, including Hawaiians themselves, shared the same ancestry. Indeed, this intimate spiritual connection with the ʻāina is fortified by Hawaiian stories of origin and genealogy, including the Kumulipo—the Hawaiian mythological chant recounting the story of creation.

"Hānau ka ʻāina, hānau ke aliʻi, hānau ke kanaka" translates to "Born was the land, born were the chiefs, born were the common people" (Pukui, 1983, p. 56). This Hawaiian proverb references the common origin of ʻāina and the Hawaiian people

and is consistent with the creation story of Papa and Wākea and the beginning of Hawaiian time. The story of Papa and Wākea explains that it was the love affair of Papahānaumoku (earth mother) and Wākea (sky father) that gave birth to the Hawaiian Islands, kalo (a staple Hawaiian food), and man, the youngest child.

The stories and proverbs presented above are just a few illustrations of the physical and spiritual/ancestral connections between Native Hawaiians and ʻāina. In this article, we highlight just one of many examples of how this intimate connection provided the basis for which several practical applications were developed within the traditional Native Hawaiian concepts of health and wellness. We also suggest that the wisdom of traditional healers likely included a mechanistic understanding for a role of the environment on physical health, a notion that may now be explained by epigenetic processes.

An Epigenetic Connection

DNA is a fundamental building block of genes that provide the instructions for making all of the parts of the human body. DNA and genes make up what is called the genome, which is identical in all cells of an individual. But DNA is only part of the story. In cells, DNA is wrapped around special proteins that together make up chromatin. Both the DNA and these proteins are naturally covered with biochemical tags, collectively known as an epigenome. Different cells in the body have different epigenomes, even though the DNA remains the same. Although the genome is fixed for life, epigenomes are flexible and respond to signals from the environment, such as diet and stress, to turn genes on or off. In addition, we recently found that the epigenome not only turns genes on or off, it also instructs which parts of DNA in the genes are recognized and used in the cell, a normal biological process known as alternative splicing (Maunakea, Chepelev, Cui, & Zhao, 2013).

The epigenome is regulated by processes called epigenetics, which comprise the study of heritable changes in phenotype that are not due to changes in the underlying DNA sequence (Maunakea et al., 2010; Waddington, 1942). There are two major epigenetic processes, both of which operate at the level of chromatin to influence fundamental cellular activities including gene transcription, chromatin structure, and DNA replication and repair. The two epigenetic processes are called histone modifications and DNA methylation. Here, we focus on one mechanism, DNA methylation, which has been studied extensively in the context of cancer.

DNA methylation involves the enzymatic addition of a methyl-group to the 5-position carbon atom of the cytosine base in DNA, most often at cytosine sites that are 5' of guanine, or CpGs (Jaenisch & Bird, 2003; Lande-Diner & Cedar, 2005; Maunakea et al., 2010). Simply put, methyl groups can be added and removed from DNA, and these changes can contribute to modulating the expression levels of genes. In fact, in cancer, DNA methylation can shut off or turn on genes that may be protective of or detrimental to normal cell activities. Studies in cancer cells show that an abnormally high degree of DNA methylation at genes can lead to gene silencing ("shut off"), whereas an abnormally low degree of DNA methylation at genes can lead to gene activation ("turn on") (Esteller, 2008). These epigenetic patterns drive the diversification of a multitude of different cell types and functions in the body and are the reason why cell diversity is possible while maintaining an identical underlying DNA sequence in an individual. A number of environmental factors can influence these epigenetic patterns and can lead to a substantial degree of epigenetic variation that can be generated pre- and post-mitotically. This epigenetic variation, governed in part by the environment, can contribute to an increased or decreased susceptibility to disease (Maunakea et al., 2010). By utilizing this body of knowledge, treatments can be made that include use of environmental factors (such as certain nutrients in a diet) to modify or reverse otherwise deleterious epigenetic patterns and decrease an individual's susceptibility to diseases. Although applications of this type within current mainstream medicine are limited and may be considered "novel," such methods have been present in the traditional Native Hawaiian practices of lāʻau lapaʻau for centuries.

Epigenetics in Traditional Hawaiian Health

Lāʻau lapaʻau is the practice of traditional Hawaiian medicine that incorporates the use of natural products, including native Hawaiian plants, to treat and prevent disease. Practitioners of lāʻau lapaʻau must have a deep connection with nature and operate within a scientific framework to be able to identify a multitude of natural resources that may aid in improving health. It can also be argued that lāʻau lapaʻau practitioners need to have a profound understanding of not only the environment as a whole, but also of their patients to be able to accurately diagnose an ailment and make recommendations for treatment. A diagnosis from a lāʻau lapaʻau practitioner includes observations of the patient's physical being as well as a

spiritual and psychological diagnosis, as all three aspects encompass the Hawaiian perspective of health (Judd, 1998). Furthermore, when diagnosing a patient who is severely sick, the traditional practice is for lāʻau lapaʻau practitioners to analyze the cause of the illness. For example, the illness may be influenced from "ma waho," the patient's outer environment, or from "ma loko," the patient's inner environment (Judd, 1998). This understanding of the relationship between environment and health used by lāʻau lapaʻau practitioners to diagnose ailments manifests an integrated scientific framework that includes the environment, a framework that is compatible with epigenetics. In traditional lāʻau lapaʻau practice, the application of this concept extends beyond the techniques used to diagnose patients and also includes strategies for treatment.

In addition to disease treatment, lāʻau lapaʻau practitioners understand the importance of disease prevention, which often incorporates a developmental context. This is exemplified by the saying, "I paʻa ke kino o ke keiki i ka lāʻau," meaning "that the body of the child be solidly built by the medicines" (Pukui, 1983, p. 136). This refers to mothers eating certain herbs (dietary supplements) prescribed by lāʻau lapaʻau practitioners during pregnancy and nursing for the sake of the baby's health during development, as well as to aid in prevention of adult-onset diseases. This proverb shows an explicit example of epigenetic concepts that were practiced in ancient Hawaiʻi and are still in practice today. By conditioning the prenatal environment with medicinal herbs, Hawaiians shape the epigenetic patterns of their children with the notion of strengthening their health throughout their lifespan. Taken together with other examples described, this suggests that the traditional Native Hawaiian concept of health is compatible with the epigenetic basis for the development, treatment, and prevention of disease. This realization inspired our hypothesis that the natural products used in Hawaiian medicine may operate through epigenetic mechanisms. Therefore, we sought to explore this hypothesis by determining whether epigenetic processes in cancer could be influenced by the lāʻau lapaʻau noni.

Noni and Cancer Treatment

Noni (*Morinda citrifolia*) can be found across the Pacific—from Polynesia and Australia to Southeast Asia—and has been widely used for more than two centuries in Polynesian traditional medicine (Judd, 1998; M. Y. Wang et al., 2002). A plant with many diverse functions, noni was grown in times of famine and war as a food crop, and different parts of the plant were utilized to treat a diverse range of ailments in traditional practices. Indeed, recent scientific research supports the traditional medicinal applications of noni by demonstrating its usefulness in a broad range of therapeutic activities. These include but are not limited to antitumor activity, immune system mediation, anti-inflammatory activity, chemopreventive, antimutagenic and antirecombinagenic activities and apoptosis-inducing effects (Brown, 2012; M. Y. Wang et al., 2002). One of the most explored areas of study concerning noni deals with its antiproliferative effects on cancer. Inspired by the teachings of kupuna Katherine Maunakea, a respected elder who shared her extensive knowledge of lāʻau lapaʻau (Teale, Lander, & Puhipau, 1994), we observed the anticancer activity of fermented noni fruit extract prepared in a traditional way (Boyd, Maunakea, Mordan, & Csiszar, 1998). Since this first report, other studies have found similar and additional activities (Brown, 2012; Li et al., 2013; Taskin et al., 2009; M. Wang et al., 1999; M. Y. Wang et al., 2002). Within the last decade, noni fruit extract has entered clinical trials to further assess its efficacy in treating cancer (Issell, Gotay, Pagano, & Franke, 2009). While there have been many studies that attempt to understand the biological mechanism by which noni acts to elicit the anticancer activities, none has yet explored whether epigenetic processes may be involved. The compatibility of the traditional Native Hawaiian concept of health and wellness with the epigenetic basis of disease inspired us to determine the role of epigenetics in the antiproliferative activities of noni in a human cancer cell line system.

Experiments that revealed links between noni and epigenetics

It was previously demonstrated that water-soluble components in aqueous extracts of the fermented noni fruit harbored antiproliferative activities in specific cancer cells. This activity was first demonstrated in a breast cancer cell line MCF-7 but did not affect the growth of other cancer cell lines, suggesting that the effects of noni are likely tumor type-specific (Boyd et al., 1998). Since this study, others have demonstrated that different noni preparations, and different parts of the noni

plant, had diverse effects on cancer (Brown, 2012). Based on historical records and ancestral knowledge of the preparation of noni among the Native Hawaiian population, fermented noni fruit was indicated as a common preparative method for anticancer applications. Therefore, we decided to test the effects of "traditional" preparations of the noni fruit on cancer cells.

We performed a study to test whether epigenetic mechanisms, in particular DNA methylation, were involved in the anticancer effect of noni fruit extract prepared in the traditional manner. This study is summarized below.

First, following a traditional Hawaiian protocol, noni fruit was collected from plants growing in the Department of Native Hawaiian Health Māla Lapa'au at the John A. Burns School of Medicine. The fruit was fermented for three days, after which we performed a water-based (aqueous) extraction. This aqueous extract was then applied to treat cells from a colon cancer line (HCT116) for a period of forty-eight hours. Live cells were counted before and after treatment and compared with control HCT116 cells growing without noni. To determine whether DNA methylation and gene expression states were altered in the cancer cells as a result of noni treatment, we harvested DNA and RNA, respectively, from noni-treated and control cells after the forty-eight-hour period. To determine whether noni caused a significant change in DNA methylation throughout the genome, we used DNA harvested from both treated and control colon cancer cells for an enzyme-linked immunosorbent assay, known as an ELISA experiment. The ELISA experiment takes advantage of an antibody specific to 5-methylcytosine (a DNA methylation modification) to measure the level of DNA methylation globally throughout the genome. To determine whether noni caused changes to gene expression states, we used RNA harvested from the same cells for real-time polymerase chain reaction (qPCR) experiments to measure the expression levels of specific genes.

Antiproliferative activities of noni in a colon cancer cell line

Consistent with previous observations of antiproliferative effects of noni treatment (Boyd et al., 1998; Brown, 2012), we observed a significant decrease in the number of live HCT116 colon cancer cells after noni treatment. This result suggests that noni inhibits the growth of these cells.

FIGURE 1. Noni treatment decreases the number of live cells. Compared with cells grown in the absence of noni (control), the number of live cells grown in the presence of an aqueous extract of noni (AE) was significantly less. Mean and standard error of the mean (s.e.m.) of triplicate experiments of total live cells counted per milliliter (mL) for control and AE-treated cells after forty-eight hours of growth are shown; the degree of statistical significance is indicated by the *P*-value displayed ($P < 0.05$), calculated using Student's t-test.

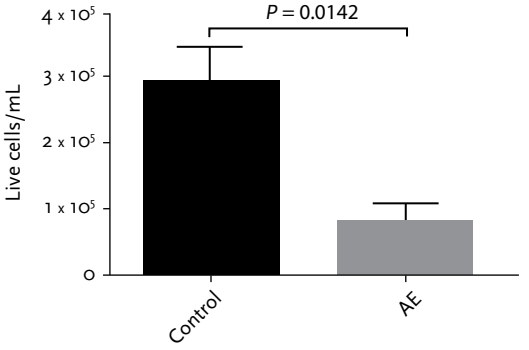
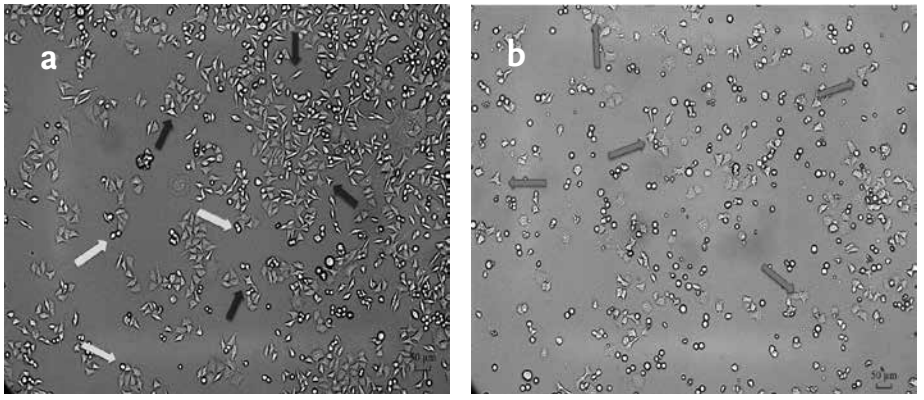


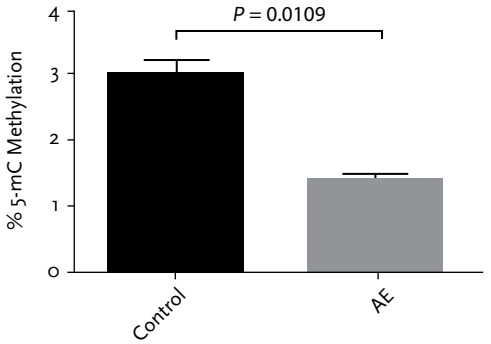
FIGURE 2. Increased cancer cell death after noni treatment. (a) HCT116 cells grown in the absence of noni (control) and imaged after twenty-four hours of growth. The four darker arrows point to examples of "healthy" HCT116 cells that adhere to the surface of the cell culture plate, whereas the three lighter arrows point to examples of "unhealthy" HCT116 cells that are detached from the surface (i.e., floating), one sign of cell death. (b) HCT116 cells treated with noni extract and imaged after twenty-four hours of growth. The arrows point to examples of cells that appear to be losing cell membrane integrity. Also note the visible increase in cell death (floating cells) and decreased adherent cells compared with that of untreated cells. These results are consistent with cell count data (fig. 1).



Noni causes global reductions in DNA methylation levels

After confirming that traditionally prepared, aqueous extracts of noni exhibited antiproliferative effects on the HCT116 colon cancer cell line, we sought to determine whether epigenetic processes, in particular DNA methylation, may have a role in this activity. Therefore, we evaluated the total genome level of DNA methylation from noni-treated and untreated HCT116 cancer cells using an ELISA experiment.

FIGURE 3. Noni treatment causes significant global loss of DNA methylation. Results from an ELISA experiment comparing the percentage of DNA methylation in the genome of untreated (control) and noni-treated (AE) HCT116 colon cancer cells. The figure shows the total level of DNA methylation (% 5-mC Methylation) measured in control and noni-treated cells after forty-eight hours of growth. Note that the reduced percentage of methylation in noni-treated cells compared with control cells was statistically significant; mean and standard error of the mean (s.e.m.) of triplicate ELISA experiments are shown; *P*-value displayed (Student's *t*-test).

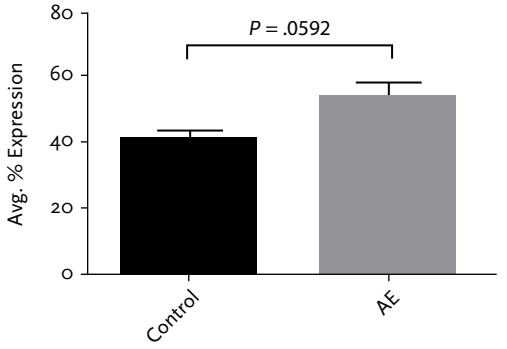


As described in figure 3, we observed a remarkable loss of DNA methylation in the genome of HCT116 cells treated with noni compared with that of untreated cells. To our knowledge, this is the first evidence that indicates noni may alter epigenetic states genome-wide.

Noni treatment causes activation of a potential tumor-suppressor gene

Because DNA methylation plays a role in turning genes on or off (gene expression states), we hypothesized that a possible consequence of the changes in DNA methylation caused by noni treatment (fig. 3) may be in altering gene expression. To determine this, we selected candidate genes for evaluating gene expression. One such gene was *YARS2*, a gene that codes for a mitochondrial protein. Using qPCR, we evaluated the expression level of *YARS2* from untreated and noni-treated HCT116 cells grown for forty-eight hours.

FIGURE 4. Noni treatment causes increased levels of YARS2 expression. Compared with untreated HCT116 cells (control), noni-treated HCT116 cells (AE) exhibit higher levels of *YARS2* expression. Mean and standard error of the mean (s.e.m.) of triplicate qPCR experiments are shown as percent expression of *YARS2* relative to the expression of a control gene, *ACTB*; the *P*-value displayed (Student's *t*-test) is close to the level of significance.



In comparison with untreated HCT116 cells, we observed higher levels of YARS2 expression in HCT116 cells treated with noni (fig. 4). While additional experiments are warranted, this result suggests that the expression level of YARS2, and potentially other genes that we have identified, may be modified by changes in DNA methylation elicited by noni treatment. Altogether, these data implicate that epigenetic processes may in fact underlie the anticancer effects of noni, at least in part. However, it remains unclear as to how significant a role epigenetic processes may be in the activities of noni on cancer and normal cells.

The compatibility between the traditional Native Hawaiian concept of health and the epigenetic basis for development, treatment, and prevention of disease formed

the basis of our hypothesis that the anticancer properties of noni involve epigenetic mechanisms. Our data described above provide initial support for this hypothesis. Further studies of this kind are warranted to understand the extent to which traditional Native Hawaiian concepts of health and wellness may include an epigenetic basis. Several insights into this inquiry could be gleaned. Establishing and reinforcing links between traditional concepts of health and wellness could have valuable translational applications into the present day. In particular, the research described here may lead to the development of culturally relevant solutions that address diseases of health disparities, such as cancer, which impact the communities from which this traditional knowledge of lāʻau lapaʻau derives.

Conclusion and Cultural Importance

The results of this study establish for the first time a link between the anticancer effects of noni and epigenetic regulation. We believe this link offers one example that demonstrates that traditional Native Hawaiian concepts of wellness included a *mechanistic* understanding for the role of the environment on physical health—a notion we now recognize as epigenetics. Research that incorporates traditional knowledge/wisdom with modern scientific tools may lead to the development of positive solutions that address diseases of health disparities in a culturally relevant context.

Cancer health disparities in Hawaiʻi

According to a report released in 2013 by the University of Hawaiʻi's Department of Native Hawaiian Health at the John A. Burns School of Medicine, "In general, Native Hawaiians and Pacific Islanders (NHPI) bear a disproportionately higher prevalence of many chronic medical conditions, such as obesity, diabetes, and cardiovascular disease, collectively known as cardiometabolic disorders...Native Hawaiians not only have higher rates of death for diabetes and heart disease but also for cancer and other leading causes of death as compared to the overall state's population" (Look, Trask-Batti, Agres, Mau, & Kaholokula, 2013, p. 9). This report shows that Native Hawaiians have a 34 percent higher incidence of death due to cancer compared with that of Hawaiʻi's population as a whole. The various applications of medicinal treatments like noni, which were used by the ancestors of

Native Hawaiians, may be used to a greater degree today to address some of these current health disparities. In addition to understanding the molecular basis of the anticancer effects of noni, this project has the potential to provide one example supporting the efficacy of Native Hawaiian medicines that could be used to directly address health disparities in the Native Hawaiian community. Indeed, clinical trials on the efficacy of noni to treat cancer provide promising results that warrant further studies (Brown, 2012; West, White, Jensen, & Palu, 2009). This success has helped to provide molecular evidence supporting the ancestral health practices of Native Hawaiians as well as the possibility for future applications of other lāʻau lapaʻau to address cardiometabolic disorders in the Native Hawaiian community.

Lāʻau lapaʻau that address cancer

In addition to noni, there are other lāʻau lapaʻau that have been implicated in cancer treatment. A study in 2000 showed that ʻawa (*Piper methysticum*) consumption reduced cancer incidence in heavy smokers (Agarwal & Deep, 2008). This initial observation has led to numerous studies that have identified active compounds in ʻawa extracts (e.g. flavokawain) that account for the anticancer effects (*Tabudravu, 2005*). Furthermore, preliminary results of ongoing research are finding that extracts from pōpolo (*Solanum americanum*), ʻolena (*Curcuma longa*), and kaunaʻoa kahakai (*Cuscuta sandwichiana*) also exhibit potent anticancer effects. Ongoing cancer research on these ethnobotanicals shows promising efficacies, especially when plant extracts consider the traditional preparations administered by lāʻau lapaʻau practioners for cancer treatment. Recent interest in traditional Hawaiian preparations of medicinal plants has prompted an ongoing investigation comparing traditional and methanolic (methanol-based extract/nontraditional) preparation of these plants. Water-based extractions of fresh plant products were used to reflect current practices of traditional preparation. Interestingly, the anticancer effects of traditionally prepared aqueous extracts were more potent than the methanolic extracts and were able to inhibit cell proliferation. While the active component and mechanism of action of these extracts are still being investigated, it is clear that pōpolo, ʻolena, and kaunaʻoa kahakai are lāʻau lapaʻau that, like noni, support traditional Hawaiian knowledge and may offer exciting new options to be used in the fight against cancer.

Importance of the role of environment in health

Mounting evidence indicates that Native Hawaiians not only understood the importance of the role of environment on health, but also incorporated this concept as part of daily living. One example we described here is their knowledge of medicines and healthcare. Also of significance are Native Hawaiians' sustainable, highly sophisticated agricultural and aquacultural systems, which offer relevant examples where optimal health of the environment integrated seamlessly with food security and nutrient-rich food production for the population. While maintaining that these systems further contributed to healthy lifestyles (Mokuau, 2011), we believe these concepts also can be transferred into current society as social determinants of health, sustainability, and environmental justice and are intimately linked with disease and health disparities (Look et al., 2013; Lepule & Kwoh, 2014). Incorporating traditional Native Hawaiian perspectives into present society may provide promising solutions to the health challenges our lāhui encounters today and may lead us to a better tomorrow. E hoʻomahalo aku kākou no nā ʻike mai kō kākou mau kūpuna a hiki ke hoʻopono i kō kākou ola kino a ke ola o ka ʻāina i kēia wā a me nā wā i mua.

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