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Introduction

“Getting to Know Cancer” is an all-volunteer, public interest, non-profit non-governmental organization focused on several of the most challenging problems in cancer research. Most recently, we initiated and led the Halifax Project, an ambitious undertaking that involved 350 scientists and physicians from 31 countries around the globe. In that effort a taskforce comprised of 12 teams of researchers worked for three years (2012-2015) on the conceptual framework for a unique and promising approach to prevent high-risk cancers, treat refractory cancers and prevent disease relapse.

Essentially the taskforce leveraged our understanding of the molecular biology of the hallmarks of cancer by combining the many targets that are emerging in precision medicine with the synergies predicted by network pharmacology. Their goal was to identify as many high-priority, synergistic molecular targets as possible along with complementary, low-toxicity protocols aimed at a “broad-spectrum” of important molecular targets. This was not intended to replace existing cancer therapies, but rather to serve as a design approach for a viable complement to traditional modes of prevention and treatment. That groundbreaking work was published in special issue of Elsevier’s Seminars in Cancer Biology in December 2015 along with a landmark capstone paper that showed that the approach should be feasible from a safety standpoint and relatively inexpensive to implement.

Given the individualized nature of many cancers, these targeted protocols will need to be tailored to the cancer type and precisely formulated to match individual genetics. While targeted therapy and personalized approaches to cancer are not new, the idea of reaching a broad-spectrum of targets is typically not feasible due to the inherent toxicity that results with many approved cancer drugs. So, the taskforce looked for evidence in the literature to support low-cost, non-toxic approaches that could be used in combination with little risk. The challenge now is to rigorously assess and report on the merits of this approach. Getting to Know Cancer plans to lead the “Broadspec” Clinical Trials, an incremental series of case studies that will grow in scale if the approach demonstrates positive results.

Initially these trials will involve a prophylactic study for myelodysplastic syndrome (MDS) patients who are at high risk of developing acute myeloid leukemia (AML) as well as therapeutic trials for advanced-stage ovarian cancer patients, pancreatic cancer patients, and glioblastoma multiforme patients. To that end, we are developing a network of licensed physicians with clinical experience treating patients diagnosed with cancer (including oncologists and functional integrative medicine physicians) to treat, support and advise cancer patients who take part in this research. If you are potentially interested in being involved in this project, please read the remainder of this document for details, and thank you for considering this opportunity. I do hope that you will choose to take part in this very important work.

Sincerely,

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**Note that bios for these advisory board members can be found at the end of this document**
Background

The Halifax Project was initiated by Getting to Know Cancer in 2011 to solve two very important challenges in cancer research. 350 scientists and physicians from 31 countries around the globe were involved in the initiative; roughly half of them were focused on low-dose exposures to chemicals in the environment, while the other half formed a taskforce that was focused on finding a better way to prevent high-risk cancers, treat refractory cancers and prevent disease relapse.

Disease heterogeneity across many cancer types makes the treatment of most cancers particularly challenging. While some important therapeutic gains have been achieved using cytotoxics and individual drugs aimed at single targets, disease relapse caused by adaptive resistance, serious side effects, and even treatment-related mortality are issues that are still frequently encountered in the clinic. Moreover, drug toxicities and multiple drug resistance issues have limited the efficacy of combination chemotherapy and severely constrained the physician’s ability pursue more than just a handful of relevant targets in refractory cancers.

However, with rapid advances in our understanding of the hallmarks of cancer, the taskforce set out to leverage this knowledge by combining the many targets that are emerging in precision medicine research with the synergies predicted by network pharmacology. Network pharmacology differs from conventional drugs by focusing on the fundamental importance of networks of interconnected biological pathways in systemic disease and recognizing that many chemicals are capable of targeting numerous proteins or networks involved in a disease. Recognizing this complexity and harnessing potential synergies is therefore a promising approach for many cancers. The goal of the taskforce focused on the development of a design framework for a non-toxic, complementary “broad-spectrum” approach to prophylaxis and therapy (i.e., one that could complement traditional modes of therapy). To accomplish this objective, the taskforce was comprised of 11 cross-functional interdisciplinary teams and a utility team – as follows:

1. Genetic Instability
2. Tumor Promoting Inflammation
3. Sustained Proliferative Signaling
4. Evasion of Anti-growth Signaling
5. Resistance to Apoptosis
6. Replicative Immortality
7. Deregulated Metabolism
8. Immune System Evasion
9. Angiogenesis
10. Tissue Invasion and Metastasis
11. Tumor Microenvironment

Within their respective areas of specialty, the teams nominated a series of high-priority molecular targets to improve patient outcomes in most cancer types. As well, they nominated corresponding low-toxicity approaches to reach the selected targets. At the same time, a twelfth team carried out a cross-validation activity to assess whether or not the chemicals selected by each of the teams had shown any contrary evidence of pro-carcinogenic potential across the mechanisms in all of the hallmark areas.

Given the toxicity of many of the traditional modes of cancer therapy, the taskforce needed to identify non-toxic, complementary constituents that could be combined without harm (to reach a broad-spectrum of targets), because patient safety was established as a top priority. Consequently, the teams nominated favored approaches that were least likely to cause harm or side effects (even when used in combination with many other approaches) and many of the substances that were selected were natural products from plants and foods (i.e., phytochemicals).
This research was published in a special issue of Elsevier’s, Seminars in Cancer Biology (2015 Impact Factor: 9.955) in December 2015 along with an all-author taskforce synthesis/capstone paper that showed that the approach should be feasible from a safety standpoint and relatively inexpensive to implement.

The Capability Gap

The practical challenge associated with implementing a complementary “broad-spectrum” approach to prophylaxis and therapy is bridging the gap between what the disease biology suggests we need and the restrictions that are inherent to the current system of cancer research and care.

Oncologists currently rely heavily on a small number of (older/legacy) cytotoxic therapies and a large number of newer targeted therapies to treat most cancer types. These drugs have all earned individual approval following several stages of successful clinical trials in which the individual drugs are tested to the brink of toxicity (for maximum dosage and effect) and to show efficacy against a particular cancer type. Once adopted, genomic and proteomic laboratory data (from individual patient’s tumor specimens) may then be used to identify therapeutic targets of relevance for the administration of these FDA-approved agents (or targeted agents undergoing approved clinical trials) which serve as the basis of the most commonly employed standard of care.

Although this approach is very rigorous, it has resulted in an inherent weakness that results in a capability gap in the clinic. When intratumoral heterogeneity is high and multiple molecular targets are relevant, there are practical limits to the number of targets pursued (due to the toxicity of these drug combinations). Additionally, there are restrictions on clinical utilization of FDA-approved cancer drugs since these therapies are typically only used for FDA-approved indications. This means the patient’s tumor must not only demonstrate the relevant molecular target(s), it must also be the specific cancer cell type designated in the FDA-approved indication. So there are instances where relevant molecular targets are identified but FDA-approved combinations are not clinically available possible that will reach a broad enough range of the known targets; and/or the therapies that are available are not approved for that cancer cell type (i.e., making such indications ineligible for payment by the payors). In these cases, clinicians must default to the limited targeted therapies available combined with older cytotoxic therapies, even though well-recognized disease relapse (caused by adaptive resistance), serious side effects, and even treatment-related mortality can result.

In some instances, this criteria can be bypassed if a physician wants to use a targeted agent (off-label) for another cancer type, but for funding reasons this is not common practice and occurs only 30 percent of the time.

The Halifax Project taskforce that focused on this issue started with a thorough review and examination of the disease biology and decided that the heterogeneity found in many cancers needed a better solution. The idea they articulated is powerful in that it builds on what we have learned from combination chemotherapy, which has shown us that mechanistic synergies are helpful. So focusing on a broad-spectrum of targets (especially in cancers that consist of many varied subpopulations of immortalized cells) is a rational clinical methodology for therapeutic implementation.

However, it does not necessarily follow that every therapeutic molecule with potential to reach a particular target must first be able to show clinical efficacy when tested on its own against a particular cancer type.
(which is currently the format for clinical trials of cancer drugs). Indeed, the actions of these chemicals on certain targets (tested on their own) may never be powerful enough to meet the standards that we have established for approving individual cancer therapies. It is true that an isolated action of a chemical on certain targets in some cancers may be adequate to slow or stop cancer (this is the basis of modern targeted therapy). However, an isolated action on other targets of relevance may still be important if our goal is to act on many different subpopulations of cells in many different ways. There are many overlapping pathways and networks of signaling in cancerous cells so some targets may simply not be adequate on their own to have a meaningful therapeutic impact against that cancer. The point of focusing on a broad-spectrum of targets is to address this issue, so when the actions of many chemicals aimed at many targets are combined, we should anticipate an impact that is greater than that which would be produced by any single chemical acting on any single target, site, or mechanism.

In other words, when we create a prioritized list of rational molecular targets for a given cancer, not all targets will be equally important, and acting on one of them alone may never produce the kinds of results we need. But if we combine two or more chemicals that are aimed at two or more rational targets in a given cancer, and we rely on dose-levels that are non-toxic, we may exert significant anti-cancer effects. The accumulation of mechanistic actions by those chemicals may still produce important anti-cancer outcomes that are greater than combined actions on any single target (due to synergistic effects).

This approach makes perfect sense as an engineered solution (i.e., given what we now know about the disease biology), but the idea of using chemicals and biological targets that have not been individually proven in clinical trials for a specific cancer type, is not the manner in which individual chemicals are currently approved for use as cancer therapies.

The Current Situation

As it stands, there is at least one promising model of combination therapy for an advanced cancer that makes use of repurposed pharmaceuticals aimed at several molecular targets. CUSP9 is a treatment protocol for recurrent glioblastoma that uses several repurposed pharmaceuticals (all widely approved by regulatory authorities and marketed for non-cancer indications). Each drug is known to inhibit one or more important growth-enhancing pathways used by glioblastoma, so the combination is intended to complement temozolomide (the cytotoxic drug used in primary glioblastoma treatment) and make treatment more effective.

Natural health products (NHPs) are also being used to support cancer therapy but not with the same sort of sophistication. Many of the drugs approved for cancer therapy by the US Food and Drug Administration (FDA) are derived from plants, including taxanes (e.g., paclitaxel) and vinca alkaloids (e.g., vinblastine). In fact, of the 98 new small-molecule anticancer drugs that were approved by the FDA between 1981 and 2010, only 20 were synthetic; the remaining 78 were either natural products (11/78) or derived from natural products (67/78). However, the lack of patentability of many natural products makes funding for clinical trials particularly challenging.

Without the monopoly protection of a patent, most manufacturers do not have enough margin and sales volume to warrant the support for clinical trials. Historically some funding for trials of individual natural products has come from the National Center for Complementary and Integrative Health (NCCIH), the American Society of Clinical Oncology (ASCO), and from individual cancer foundations. Trials using single-agent interventions with common dietary supplements have failed to produce the kinds of outcomes
needed, but evidence continues to accumulate that supports the mechanistic potential of many NHPs and their potential relevance for cancer, so combinations of NHPs are still a promising way forward. There are many instances of promising phase 2 trials, but these trials are often not followed up by phase 3 trials, which is likely because the manufacturers see positive phase 2 trial outcomes as being sufficient for product promotion (without having to fund a randomized, placebo-controlled phase 3 trial). As a result the FDA has not yet approved any dietary supplement or food to prevent cancer, halt the growth of cancer, or prevent cancer recurrence.

The formal use of NHPs in conjunction with conventional treatment is referred to as integrative oncology and there are many practitioners in this category. In general, the most common integrative oncology modality of interest to cancer patients relates to NHPs as complementary therapeutics to arrest their cancer. However, the evidence base is much stronger for the treatment of cancer-related symptoms (e.g., acupuncture for nausea, exercise for sleep, anxiety etc.), so in many clinics the patient’s interests are often not aligned with the complementary support that is available. Also, even though integrative oncology programs in many clinics now offer nutritional counseling, meditation, lifestyle alterations, reflexology, acupuncture, homeopathy, etc. (to support cancer patients and improve outcomes), the scientific evidence supporting these complementary practices is not always strong, so even these practices have had considerable critique.

Nonetheless, a recent survey of clinics in Washington State used data provided by oncology board certified Fellows of the American Board of Naturopathic Oncology to show that more than 72 oral or topical, nutritional, botanical, fungal and bacterial-based medicines had been used during the first year of care of the female breast cancer patients studied (n=324). This gives a sense of the number of NHPs used in the clinic to complement conventional treatment, but how these supplements are selected and combined varies considerably by practitioner. While physicians engaged in Integrative Medicine and Functional Medicine are accustomed to treating patients diagnosed with cancer utilizing multiple NHP supplements and (some) pharmaceutical medications, most physicians remain largely unfamiliar with cancer molecular signaling pathways and networks (c.f Gray et al.), so their choices are not being guided by the best science available.

Consequently, genomic and proteomic assessments are currently not being used to greatest anti-cancer clinical potential, because typically only one high priority target is used and that is only when FDA approved therapies exist for that particular target and that particular cancer type. This is not antagonistic criticism of the way in which we approve individual cancer therapies. Rather it simply shows how our reliance on individual therapies for specific cancer types is now out of step with our understanding of what we know is needed to tackle the complexity of the disease biology found in many advanced cancers.

Despite these limitations, the use of NHPs among cancer patients is widespread, with 20-90% of them using supplements - yet roughly half of them do not share this detail with their treating physician (because they feel their physicians are not knowledgeable, or will be indifferent or negative toward their use). Recognizing that the majority of patients undergoing cancer therapy now use NHPs (many without consulting their physician), the Clinical Practice Committee of The Society of Integrative Oncology, which consists of leading researchers and clinicians who have experience in using supplements, recently developed a list of useful supplements for physicians. They provided basic information, such as evidence on effectiveness, clinical trials, adverse effects, and interactions with medications to give physicians and other health care providers up-to-date information so they could discuss realistic expectations, potential benefits and risks associated with these supplements. The list included curcumin, glutamine, vitamin D, maitake mushrooms, fish oil, green tea, milk thistle, astragalus, melatonin, and probiotics. However,
while this is certainly important information to share, given that most patients and most physicians don’t have a detailed understanding of cancer biology, it just doesn’t move us far enough in the right direction to capitalize on the therapeutic potential that a broad-spectrum methodology should be able to deliver.

In some ways, it is ironic that we are at a juncture where our rigorous approach to developing the very best individual therapies, is constraining our ability to approach treatment in the manner that is needed. Cancer chemotherapy began with crude cytotoxic therapies and has evolved to targeted therapies (once we began to understand the biology of the disease) and now the push is towards precision medicine, which uses more advanced diagnostics (e.g., next-generation sequencing technologies) to look for changes in tumor DNA, RNA and proteins. This precision gives the clinician the ability to improve the selection of therapies which target particular molecular abnormalities, which is an appealing concept in principal but it is particularly difficult to implement in advanced cancer.

For example, in metastatic breast cancer, the identification of driver mutational events is a major clinical challenge. The field remains largely focused on single targets and once the canonical targets for a given cancer (e.g. in this case ER, HER2, PIK3CA and AKT1) are exhausted, finding additional oncogenic “drivers” is difficult. This is a profound challenge that we face in most advanced cancers. The Halifax Project taskforce that focused on this problem envisioned that we could solve this issue by using a wide range of targets that are key to disabling the mechanisms of the hallmarks of cancer. This takes the emphasis away from finding oncogenic drivers and instead focuses on key events that could disrupt the many inter-related networks and signaling pathways that enable all aspects of cellular immortalization. So we have a conceptual approach to solve the problem, but how do we now reach many targets simultaneously (when we have a limited set of individual therapies approved for cancer treatment in any given cancer type)?

The solution that was articulated in the Halifax Project suggests a focus on NHPs, repurposed pharmaceuticals, and other chemicals that are readily available, well tolerated and known to have the sort of mechanistic anti-cancer potential that is needed for the targets which are relevant in any given cancer type. This sort of a broad-spectrum methodology would better exploit genomic and proteomic assessments because clinicians could aim to reach a much greater number of relevant targets simultaneously. On an individual case-by-case basis, this will involve the identification and selection of relevant therapeutic targets and options (i.e., relevant re-purposed pharmaceuticals and NHPs that have potential to reach the targets that are relevant for a given cancer) and it would be constrained by the practical availability of the various pharmaceuticals and NHPs of interest.

The heterogeneity that exists in most advanced cancers outstrips the capabilities of many approved therapies, so it demands a much more robust therapeutic solution and this is a problem of significant proportions. Yet the development of this sort of a protocol is simply not going to be possible in most clinics without expert support because most physicians do not have the training to understand how NHPs and repurposed pharmaceuticals might be used to reach important molecular targets. Some oncologists might have the requisite knowledge but most will not be willing and/or able (due to medical-legal restrictions) to implement therapeutic options beyond the existing standard-of-care. By contrast, there are functional and integrative medicine physicians who would be willing and able to implement multi-agent therapeutics aimed at a broad-spectrum of targets (i.e., in support of, and in addition to, conventional FDA-approved cancer treatments), but most will not have the knowledge to develop such a protocol.

For this reason, the Broadspec project has been initiated. Our goal is to demonstrate that the use of a broad-spectrum method will produce unique protocols for each cancer patient that will improve their overall chance of achieving cancer control and remission, significantly improve their quality of life and
significantly extend their duration of survival (compared to similar patients undergoing only conventional therapy and not supported by this method). This possibility is well-supported conceptually but it has not yet been demonstrated in systematic clinical research.

To that end, we intend to organize and assist functional integrative medicine physicians who are willing and able to implement multi-agent therapeutics in addition to, conventional FDA-approved cancer treatments administered by patients’ medical oncologists and radiation oncologists. This will bring rigor to the manner in which repurposed pharmaceuticals and NHP supplements are administered to cancer patients in their practice, because we will help these physicians develop safe, personalized, broad-spectrum precision medicine protocols optimally designed for their individual patients. Initially, this assistance will be offered to a very small number of physicians who are treating or supporting cancer patients across several cancer types. As positive outcomes in these individual case-studies are demonstrated, a greater number of cases will be considered.

Cancer Types

We have identified four cancer types for the Broadspec project that will be supported in initial case studies. This effort will involve expert support and guidance (in the development of broad-spectrum support protocols) for physicians who are treating (1) myelodysplastic syndrome patients who are at high risk of developing acute myeloid leukemia (AML); (2) advanced-stage ovarian cancer patients; (3) advanced-stage pancreatic cancer patients; and (4) glioblastoma multiforme patients.

Each of these cancer types is explained in a bit more detail below:

**MDS patients at high risk of developing AML**

Myelodysplastic syndromes are a heterogeneous group of clonal stem cell disorders with an inherent tendency for leukemic transformation. High and Very High risk MDS patients (defined by the International Prognostic Scoring System), compromise a third of MDS patients\(^{28}\) and have a median survival of 1.6 and 0.8 years, respectively\(^{40,41}\).

Currently Food and Drug administration (FDA)-approved drugs for the treatment of MDS are not curative and their effect on survival is limited. These medications include the hypomethylating agents azacitidine and decitabine and also lenalidomide (for MDS with isolated del(5q)). To date, allogeneic stem cell transplant remains the only treatment option for possible cure\(^{42}\), but many patients are not eligible for transplantation due to advanced age, or associated co-morbidities\(^{43}\).

About one-third of patients with MDS progress to MDS-related acute myeloid leukemia (secondary AML), an aggressive stem cell malignancy characterized by ≥20 % bone marrow (BM) blasts\(^{43}\). The remaining two-thirds normally succumb to progressive bone marrow failure which leads to bleeding (due to low platelet counts), recurrent infections (due to low white blood cells), and severe anemia (which requires regular transfusions and causes iron accumulation and toxicity)\(^{44}\). For MDS patients who do progress to secondary AML, the outcome is generally grave. Cytotoxic chemotherapy has been the most common form of treatment for the past 20 years so clinical outcome remains poor for the majority of patients\(^{45}\). Indeed, most patients are resistant to treatment and the long-term survival rate of treated patients is <10%\(^{44}\).
So a broad-spectrum prophylactic intervention that could prevent a transition to secondary AML in MDS patients would be a welcomed advance. Moreover, other targets of relevance in myelopoiesis have been identified which has spurred the development of agents for MDS (e.g., immunomodulatory agents, immunosuppressive therapies, survival signal inhibitors, thrombopoiesis-stimulating agents, pharmacologic differentiators, and anti-angiogenic and apoptotic agents) so there are many additional targets that could also be incorporated in a broad-spectrum protocol developed specifically for MDS patients.

**Advanced-stage ovarian cancer**

Advanced stage ovarian cancer is a disease with a high relapse rate. People with ovarian cancer can be largely asymptomatic in early stages, so more than 75% of patients are diagnosed in an advanced stage of disease (International Federation of Gynecology and Obstetrics stages III–IV). Surgery and chemotherapy (using taxanes and platinum compounds) can reduce tumor burden and extend survival times, but recurrence rates are higher than 80% in advanced stage patients. Platinum-resistant ovarian cancer can be treated with cytotoxic chemotherapy (e.g., paclitaxel, topotecan, pegylated liposomal doxorubicin, and gemcitabine), but there are no curative treatment options for refractory forms of the disease so the median survival time of patients with advanced stage disease is 65 months.

A significant number of studies have provided insights into the molecular pathogenesis of this cancer, which can now be divided into four-groupings: i) high-grade serous carcinomas; ii) endometriosis-related tumors that include endometrioid, clear cell, and seromucinous carcinomas; iii) low grade serous carcinomas; and iv) mucinous carcinomas and malignant Brenner tumors. As a result, a good number of rational targets have been identified and targeted therapies have shown promising results in ovarian cancer clinical trials, including treatments targeting the vascular endothelial growth factor pathway (e.g., bevacizumab and aflibercept), DNA repair mechanisms (e.g., iniparib and olaparib), and folate-related pathways (e.g., pemetrexed, farletuzumab, and vintafolide). So there is a shift in focus to treatments that are more subtype-specific and a belief that more robust combinations of selected actions on relevant targets (in concert with taxanes) may prove to be more effective, making this a cancer that might benefit from a broad-spectrum methodology.

**Advanced-stage pancreatic cancer**

Pancreatic cancer is the third leading cause of cancer-associated deaths in the United States. In the USA alone, approximately 53,670 people will be diagnosed with pancreatic cancer and nearly 43,090 will die from the disease in 2017. Surgical resection is usually the only chance of a cure for pancreatic cancer but given that the disease is often diagnosed in late stages, only 15%–20% of patients with pancreatic cancer are eligible for surgical resection, and the cancer frequently recurs even after complete surgical resection. Consequently, the median overall survival for pancreatic patients is just 2–8 months, with a five-year survival rate of 7.7%.

Over the past few decades, the standard drugs for pancreatic cancer were 5-fluorouracil (5-FU) and gemcitabine. Historically the success rate of 5-FU was <20% but gemcitabine offered marginally better results so it is now prescribed for the patients suffering from locally advanced (stage II or stage III) or metastatic (stage IV) pancreatic cancer. Recently, first-line therapy with gemcitabine plus nab-paclitaxel or a regimen of fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) has increased the median overall survival to 8.5 months and 11 months, respectively, in patients with metastatic pancreatic cancer.
This is compared to an overall survival of only 6 months prior to 2011 and the sequencing of the two regimens mentioned above has improved median overall survival to 18 months.

Although there are multiple subtypes, the most common tumor type among pancreatic cancers is pancreatic ductal adenocarcinoma (PDAC) and the emerging molecular taxonomy of PDAC supported by next generation sequencing analyses is creating new opportunities to personalize therapeutic approaches. However, the translation of treatment based on multiple unique targets is presenting considerable challenges in the clinic. The results from genomic testing can take several weeks (causing unacceptable treatment delays), biopsies are not always possible, and patients are not always strong enough for this approach using existing therapies.

Molecular targeted therapy has been extensively evaluated in pancreatic adenocarcinoma, but with very little improvement to survival. Prospective randomized trials of irinotecan encapsulated in liposomal-based nanoparticles and other combination regimens have resulted in some improvement to patients' outcome (as second-line therapy after disease progression) but durable responses are still rare. Most recently, pegylated recombinant human hyaluronidase (PEGPH20), a novel agent that degrades hyaluronic acid (a major component of the extracellular matrix), has been used to target the tumor stroma. This approach has shown some promise in clinical trials and Phase 2 and 3 trials of PEGPH20 plus chemotherapy are ongoing (with outcomes eagerly anticipated).

At the same time, many NHPs have been tested in experiments designed to support conventional approaches to therapy in pancreatic, and several have been credited with improving the immune system, suppressing tumor progression, enhancing beneficial effects, and lessening adverse/side effects of chemotherapy and radiotherapy. So, a more global integrative approach incorporating immunotherapy, cytotoxic chemotherapy and NHPs should have a greater potential for efficacy and also provide support for other treatment-related effects as well.

**Glioblastoma multiforme**

Glioblastoma multiforme (GBM) is the most malignant primary brain tumor in adults and the most common astrocytoma and classified as World Health Organization grade IV. Each year, about 5-6 cases out of 100,000 people are diagnosed with primary malignant brain tumors, of which 80% are malignant gliomas, and half are GBM. GBM is highly malignant and typically accompanied by extensive infiltration into the surrounding tissue. GBM often infiltrates the brain in ways that limit the potential effectiveness of surgical resection. Surgery is typically followed by a combination of radiotherapy with concurrent and adjuvant chemotherapy (i.e., temozolomide), but median survival is only about 15 months.

Progress over the past decade has revealed many complex genetic alterations and genomic profiles (epigenetic and genetic alterations as well as gene/protein expression profiles) in primary and secondary tumors and in the tumor microenvironment. This has led to the first molecular/genetic classification of the disease and four well-defined genomic subtypes of GBM (i.e., classic, mesenchymal, proneural, and neural). So several targeted therapies have been evaluated in clinical trials, but to date, only a single anti-angiogenic agent (bevacizumab) has been approved for the treatment of recurrent GBM in the United States and Canada.

Consequently, with their rapid diffusion, infiltrative growth and high level of cellular heterogeneity, GBM, is one of the most refractory and lethal human cancers. A broad-spectrum methodology would allow
us to leverage our knowledge of the many potential targets that appear to exist in these complex cancers and give us a much better chance of addressing this heterogeneity.

The Broadspec Project

The first step taken towards the initiation of the Broadspec project was the formation of an esteemed advisory board with expertise spanning the various aspects of the project that is envisioned. As a result, the current advisory board has experts in the molecular biology of the four types of advanced cancers mentioned, experts in cancer biology, and experts who have extensive clinical experience using NHPs and repurposed pharmaceuticals. The advisory board will therefore serve a key role as they will help steer this project forward. In addition, the following sections provide an overview of the planned approach for the Broadspec Project.

Ethics

One of the biggest challenges in this project will be the challenge of getting ethics board approval for a series of case-studies using a common methodology that utilizes varying combinations of therapeutics (as opposed to a single therapeutic regimen for a single cancer type).

Historically, cancer therapeutics have been tested one at a time for individual efficacy before considering these an individual therapy as a potential constituent for a combination chemotherapy regimen. Also, because of toxicity constraints, combinations of substances have almost always consisted of a very limited number of chemicals. As well, cancer types in clinical trials are often defined by cell type. They are sometimes further characterized by cancer stage, and occasionally refined further by dominant form of an important genetic mutation (e.g., ER-positive). So a broad-spectrum methodology (which is based on our current understanding of disease biology) will challenge several of these norms.

For example, we will focus on cancers that are defined by cell-type and cancer stage, but the genetic and proteomic information that will be gathered in each individual case will result in a substantial list of potential targets that will be unique to that particular patient. As the hallmarks of cancer disease framework suggests, some of these targets will be tumor specific while other relevant targets are found in related systems and the tumor microenvironment (involving processes such as inflammation, angiogenesis, immune-evasion, tissue invasion and metastasis, etc.). As such, there will be a long roster of potential therapeutics to be considered (i.e., repurposed pharmaceuticals and NHPs which might have the potential to reach these targets).

These agents can be identified in the literature but the criteria by which they are chosen will need to be carefully defined. The standard of evidence for potential actions by an agent, combined with issues related to practical availability, and details on safety and tolerance, will all be critically important. This will result in unique combinations of dozens of common agents being combined to produce a personalized protocol for each patient. Each constituent that is selected will therefore need to have a very broad therapeutic index, and these constituents will need to be introduced individually and incrementally in the clinic (such that the number of agents being used in combination increases over time) with close monitoring by a physician to assess tolerance and quickly identify any adverse effects.

This idea of a personalized protocol of agents aimed at a broad-spectrum of targets represents a fundamental and paradigmatic shift (in comparison to single chemicals or static combinations that are put
forward for general purpose use across a broad base of patients with the same cancer type). This approach recognizes that addressing the heterogeneity in most advances cancers is going to take more than a predictable action on a few key driver mechanisms. It also recognizes that some agents that have the potential to exert an action on a specific mechanism of relevance may not be potent enough to gain approval as an individual therapy but still serve a valuable support role in a combination approach.

Currently, Ethics Boards do not typically favor great numbers of chemicals in combination for cancer therapy, but the current situation is unsatisfactory. On the one hand, we have oncologists who understand the disease biology but ignore the potential value of additional actions and synergies that could be produced by complementary agents (because these agents have not been individually proven or approved as cancer therapies). Yet 20-90% of patients are using NHPs anyway (many of whom are not sharing this detail with their treating physician)\textsuperscript{35,36} and other physicians are supporting cancer patients with repurposed pharmaceuticals and NHPs without a thorough knowledge of disease biology. So the false wall that currently divides these practitioners is truly a fiction that should not be allowed to stand. It serves only as an impediment to a practice of supplementation that is already being widely employed.

What is now needed is a rigorous set of trials that can determine whether or not patients with advanced cancers who are undergoing conventional forms of treatment would benefit from a personalized, broad-spectrum protocol that has the potential to also act upon as many additional targets as possible. Currently these patients are trying to supplement themselves (i.e., without physician support) or they are working with physicians who are not using the best information available to make decisions related to the types of constituents that might work best given the genetic makeup of the cancer. As a result, these ‘experiments’ are not based on the best science available, and the patient outcomes from these efforts are not peer-reviewed or published. Our task is therefore to convince an Institutional Review Board that this situation is untenable. We need to explain why the current situation demands a much more rigorous form of systematized investigation.

The World Medical Association Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) 2013 contains a new provision that addresses these circumstances. With respect to “Unproven Interventions in Clinical Practice”, clause 37 reads as follows:

\begin{quote}
37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.
\end{quote}

So our goal is to create the sort of support that is needed to provide the expert advice that physicians will need to offer protocols that are highly personalized to individual cancers using a rigorous, reproducible method and to cooperate with those physicians such that the progress of these patients can be carefully documented and the results published. Since every patient will have a tailored protocol, our goal will be to produce a case-series that can capture these results over time.
The Physician Network

The Broadspec project will use a project website at [www.broadspec.org](http://www.broadspec.org) to generate visibility for this initiative and we will recruit collaborating physicians for each of the four cancer types described above. Since the project will get underway with a very small number of patients as initial cases, these physicians will be hand selected and recruited based on their interest in the project and their clinical experience.

Provided the clinical results in the early cases are encouraging, a broader outreach will then be undertaken and an “Expressions of Interest” page on the website will be used to help us further expand the number of collaborative relationships that we have with physicians who can take advantage of these trials.

Project Funding

This project is not funded externally, so physicians who are interested in taking part in this project will not receive compensation for their participation. However, collaborating physicians will receive individualized case-related guidance, including recommendations and rationale for a personalized therapeutic protocol and detailed guidance/advice for ongoing patient management (provided the physician has at least one patient that meets the project criteria for inclusion). Collaborating physicians will be responsible for the patient relationship, all clinical decisions, case documentation, and for sharing details of case management and outcomes (i.e., when it comes to publishing the results).

At the same time, patients will need to pay the fees are normally levied by that particular physician for treatment and also any costs related to the medications that are recommended or prescribed.

Project Outcomes

We are currently recruiting physicians who have experience treating and supporting patients with any of the cancer types mentioned above. For those who are interested in the Broadspec Project, it is an opportunity to be part of an important initiative that has the potential to be groundbreaking. These cancers are incredibly challenging and complex, but our understanding of these diseases is advancing quickly and we are rapidly gaining new knowledge so we believe that the timing is right for this unique approach. With a strong advisory board and a solid network of knowledgeable clinicians/physicians involved, we are confident that something truly extraordinary will result.

Expressions of Interest

If you are potentially interested in participating in the Broadspec Project, please submit an expression of interest form online at [http://www.broadspec.org/collaboration.php](http://www.broadspec.org/collaboration.php)

References


Professor of Medicine-Oncology and of Pathology at Stanford School of Medicine, Stanford University, California, USA. Dr Felsher’s research interests include both basic science and translational research studies that investigate how oncoproteins initiate and sustain tumorigenesis. He is an elected member of the American Society for Clinical Investigation and the Association of American Physicians. He is the founding Director of the Stanford Translational Research and Applied Medicine (TRAM) Program, Director of Oncology Research and Director of Admissions of the Stanford Medical Scientist Training Program. His laboratory has developed unique model systems to demonstrate that cancer is reversible upon oncogene inactivation. Dr. Felsher has published over 150 papers and chapters, and has been invited to speak over 200 international seminars and symposia. Dr. Felsher also was a team leader in the Halifax Project and he led two teams that were focused on the tumor microenvironment.

Founder of the Integrative Medicine Program at Greenwich Hospital-Yale Health Systems (1998) and now Director of Nutritional Oncology, Assistant Clinical Professor, the Director of Curriculum in Nutrition, and the Director of Curriculum of Integrative Medicine at Yale School of Medicine. Dr Boyd is an oncologist and hematologist who has been a practicing medical oncologist since 1993. Dr. Boyd is a pioneer in the field of integrative cancer care, with a targeted focus on nutritional support for cancer patients. Incorporating emergent, evidence-based medical oncology with cancer-specific nutritional counseling, he combines comprehensive support for the healing process. Dr. Boyd is the founding president of the Integrative Cancer Care Research Foundation and a board member of Environment and Human Health, Inc., a nonprofit organization made up of physicians and public health professionals dedicated to the purpose of protecting health from environmental harms.

Dr LaValley combines state-of-the-art molecular biology with complementary approaches to treatment. Importantly, he has developed highly sophisticated and rapid data-mining approaches that can link evidence-based targeted therapeutic interventions to the molecular biology of cancer. Dr. LaValley has been treating patients for over 28 years and since 1988 he has been a medically licensed by the Texas Medical Board and the College of Physicians and Surgeons of Nova Scotia while also serving as a professional consultant to other physicians (i.e., he develops advanced, evidence-based, molecularly-targeted treatment plans and recommendations for physicians to receive, consider, and administer to patients diagnosed with various types of cancers). Dr LaValley served in the antecedent Natural Health Products Advisory Panel and National Transition Team for the Office of Natural Health Products within Health Canada from 1997 – 2000 and was also a member of the Canadian National Advisory Group on Complementary and Alternative Medicine, Health for Health Canada from 1998 – 1999. He was appointed by the Minister of Health to the Expert Advisory Committee of the Natural Health Products Directorate for the development of Regulations for Natural Health Products in Canada from 2000 – 2004. He is a member of the American Medical Association, the Texas Medical Association, the Canadian Medical Association (CMA), the College of Family Physicians of Canada, and he has been a member of the Society for Integrative Oncology since it began in 2003.

Research Associate at Harvard TH Chan School of Public Health and Honorary Reader at University College London. Dr. Retsky received his PhD in Physics from University of Chicago in 1974 and made a career change into cancer research 30 years ago. He was on Judah Folkman’s staff for 12 years. He is a 22 year survivor of Stage IIIc colon cancer and noted for opting not to use conventional maximum tolerated adjuvant chemotherapy, and instead was the first person to use what is now called metronomic chemotherapy. It was non-toxic and apparently worked. He is currently interested in perioperative NSAIDs to reduce early relapses in cancer. Current activity is to raise money for a clinical trial of perioperative NSAID to treat triple negative breast cancer in Nigeria. He is a Founder and until just recently was on the Board of Directors of Colon Cancer Alliance and he has published more than 70 papers in physics and cancer. He is editor of a book published in July 2017 on the cancer project for Springer/Nature (“Perioperative Inflammation as Triggering Origin of Metastasis Development”).
Asfar S. Azmi, PhD
Wayne State University

Assistant Professor in the Department of Oncology, Wayne State University School of Medicine, Detroit, Michigan USA. Dr. Azmi has more than a decade of experience in the area of small molecule drug development against important cancer targets such as Bcl-2, Mcl-1, nuclear exporter protein CRM1 and p21 activated kinase 4 (PAK4). Dr. Azmi’s work has led to the clinical translation of a number of cancer drugs such as CRM1 inhibitor Selinexor and recently the PAK4 inhibitor KPT-9274. He has published >100 peer reviewed articles and numerous thematic volumes in the area of cancer drug discovery. He is the author of multiple cancer drug discovery books and is also the Editor in Chief of the journal Oncobiology and Targets. He has received numerous young investigator awards from premier scientific bodies such as American Association for Cancer Research and American Pancreatic Association. His lab is well funded by the National Cancer Institute, National Institute of Health and by the pharmaceutical industry.

Gloria Huang MD
Yale University

Associate Professor of Obstetrics, Gynecology & Reproductive Sciences: Gynecologic Oncology at Yale Medicine, Connecticut, USA. Dr. Huang is an internationally known expert in the treatment and prevention of ovarian, uterine and cervical cancers. Dr. Huang is skilled at minimally invasive surgery and is the principal investigator of a federally funded cancer research laboratory. A board-certified gynecologic oncologist, Dr. Huang enjoys providing exceptional, individualized, comprehensive care to patients, bringing together multi-disciplinary clinical teams to achieve the best outcomes. She is passionate about advancing the field of gynecologic oncology through innovative scientific research and hopes her discoveries will lead to better treatments for patients.

Barbara Vanderhyden, PhD
The University of Ottawa

Corinne Boyer Chair in Ovarian Cancer Research at The University of Ottawa, in Ontario, Canada. Barbara Vanderhyden completed her Ph.D. in Reproductive Physiology at the University of Western Ontario in 1988. She then did postdoctoral studies at The Jackson Laboratory in Maine, where she learned to climb mountains, both literally and scientifically. In 1991, she joined the Cancer Research Group at the University of Ottawa, which has evolved into the Cancer Therapeutics Program at the Ottawa Hospital Research Institute, where she is a Senior Scientist. Dr. Vanderhyden is also a Professor at the University of Ottawa and has held the inaugural Corinne Boyer Chair in Ovarian Cancer Research since 2000. She established and ran the university’s transgenic mouse facility for 14 years

Nuzhat Ahmed, PhD
The Fiona Elsey Cancer Research Institute

Inaugural John Turner Professorial Cancer Research Fellow, The Fiona Elsey Cancer Research Institute, Adjunct Professor, Research & Innovation, Federation University Australia, Ballarat, Australia. Dr Ahmed is an experienced cell and molecular biologist with a longstanding interest in understanding the molecular mechanisms of ovarian cancer spread. She did her postdoctoral research training in Malaghan Institute of Medical Research, Wellington, New Zealand, University of New Castle, Australia and University of British Columbia in Canada. From 2002-2014, Dr Ahmed led the Ovarian Cancer Research Group in Women’s Cancer Research Centre, Royal Women’s Hospital, Melbourne and currently leads the Ovarian Cancer Research Program in Fiona Elsey Cancer Research Institute, in Victoria, Australia. As chemoresistance associated with recurrence after chemotherapy treatment is the major cause of mortality in women with ovarian cancer, Dr Ahmed’s current work is focused in understanding the mechanisms of survival of ovarian cancer cells in response to chemotherapy treatment and re-growth of these cells to cause clinical recurrence. These studies have utilized isolated tumour cells (primary, and also from ascites) from patients diagnosed with the advanced-stage disease before and after chemotherapy treatments and also animal models to model profiles of genes/proteins associated with chemotherapy resistance.
Dr. Raza is the Director of the MDS Center in the Division of Hematology and Oncology at Columbia University in New York, NY. Dr. Raza completed her medical education in Pakistan, training in Internal Medicine at the University of Maryland, Franklin Square Hospital and Georgetown/VA Medical Center in Washington, D.C. and her fellowship in Medical Oncology at Roswell Park Cancer Institute in Buffalo, New York. She started her research in Myelodysplastic Syndromes (MDS) in 1982, moved briefly to Cincinnati, Ohio and then to Chicago, Illinois in 1992, where she established a highly productive translational research program in MDS. This program, along with a Tissue Repository containing more than 40,000 samples from MDS patients was successfully relocated to the University of Massachusetts in 2004 and to St. Vincent’s Comprehensive Cancer Center (SVCCC) in 2007. Before moving to SVCCC, Dr. Raza was the Chief of Hematology at the University of Massachusetts in Worcester. Dr. Raza’s basic research has been strictly therapy-driven and is marked by her tireless efforts to move the advances in the laboratory to the bedside with alacrity for the improvement of treatment outcome of MDS patients. She is well known internationally for several landmark observations related to the biology and treatment of MDS and she has published the results of her laboratory research and a large number of clinical trials in prestigious, peer reviewed journals such as The New England Journal of Medicine, Nature, Blood, Cancer, Cancer Research, British Journal of Hematology, Leukemia, Leukemia Research (250 full-length papers, 15 book chapters, 510 abstracts, and editor of a book devoted to MDS).

Senior staff oncologist at the Josephine Ford Cancer Center and Adjunct Assistant Professor, University of Michigan. Dr. Khan completed her residency and fellowship training at the university of Michigan health system. She then continued as faculty there and did translational research under the mentorship of Dr. Diane Simeone working on chemo-resistance mediated via Notch signaling in pancreatic cancer. Dr. Khan is the recipient of a "Career development Award" from the NCI/CTEP for the clinical development of a novel Notch inhibitor in pancreatic cancer. Dr. Khan's current research focus lies in the clinical development of novel therapeutic strategies for the treatment of pancreatic cancer. At Henry Ford, Dr. Khan is the medical director of the pancreatic oncology program and is the recipient of the Mort Harris grant for pancreatic cancer research. Dr. Khan has conducted several clinical trials using novel agents in pancreatic cancer.

Dr El-Rayes is an Associate Professor at the Emory University School of Medicine, Director of the GI Oncology Translational Research Program at the Winship Cancer Institute and Medical Director of the Clinical Trials Office at the Winship Cancer Institute. Dr. El-Rayes completed his internal medicine residency at Wayne State University, the hematology oncology fellowship program at the Wayne State University and then was an Assistant Professor (GI oncology) involved in translational pancreatic cancer research. Dr. El-Rayes joined Emory University in September 2009 and is designated as a Distinguished Cancer Scholar by the Georgia Cancer Coalition.

Dr. Lyssiotis is an Assistant Professor at the University of Michigan Medical School with appointments in the Departments of Physiology and Medicine. His lab, located in the UMHS Comprehensive Cancer Center, studies the biochemical pathways and metabolic requirements that enable tumor survival and growth and, in particular, how this information can be used to design targeted therapies. Among his many contributions, Dr. Lyssiotis has defined several new metabolic pathways in pancreatic cancer cells and tumors that are required for growth. For this work, he has been awarded the Dale F. Frey Award for Breakthrough Scientists, the Tri-Institutional Breakout Prize for Junior Investigators and the American Gastroenterological Association Augustyn Award in Digestive Cancer. He is also a Sidney Kimmel Foundation Junior Scholar, a Lefkofsky Family Foundation Scholar, a Melanoma Research Alliance Young Investigator and a V Foundation Junior Scholar.
Tenured Professor of Pathology, Microbiology, and Immunology, University of South Carolina School of Medicine, Columbia, SC, USA. Dr Ray’s research interests include the understanding of the histological, cellular, and molecular mechanisms of pathogenesis of malignant diseases, with a special emphasis on glioblastoma, and development of novel therapeutic strategies for their treatments in preclinical models. Dr. Ray’s research has been funded by Federal, State, and Private funding agencies. He has served in NIH, NSF, and DoD study sections as well as in State, Private, and International grant review panels. Dr. Ray serves as editorial board member in many biomedical journals. He has presented 318 abstracts in national and international scientific meetings and published 26 book chapters and 194 peer-reviewed papers. Also, he has edited 2 books and 2 journals. Dr. Ray has trained many undergraduate and graduate students, postdoctoral fellows, and junior faculty members in his laboratory.

Dean of Studies, International Initiative for Accelerated Improvement of Glioblastoma in Vermont (United States) – Dr Kast’s research in recent years has been devoted to publishing work on identifying and understanding growth-promoting or cell-death resisting mechanisms in glioblastoma, then searching for drugs that are marketed for other indications, that would inhibit or interfere with these paths. As examples: the anti-hypertension drug captopril inhibits MMP-2 & MMP-9, the anti-alcoholism drug disulfiram inhibits function of stem cell mediator ALDH, the anti-fungal drug ketoconazole inhibits 5-lipoxygenase and thromboxane synthase, the anti-HIV drug nelfinavir (or ritonavir) inhibit HSP90. All these targets were previously identified as important facilitators of glioblastoma growth.