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## A Broad-Spectrum Integrative Design for Cancer Prevention and Therapy

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### Abstract

Targeted therapies and the consequent adoption of “personalized” oncology have achieved notable successes in some cancers; however, significant problems remain with this approach. Many targeted therapies are highly toxic, costs are extremely high, and most patients experience relapse after a few disease-free months. Relapses arise from genetic heterogeneity in tumors, which harbor therapy-resistant immortalized cells that have adopted alternate and compensatory pathways (i.e., pathways that are not reliant upon the same mechanisms as those which have been targeted). To address these limitations, an international task force of 180 scientists was assembled to explore the concept of a low-toxicity “broad-spectrum” therapeutic approach that could simultaneously target many key pathways and mechanisms. Using cancer hallmark phenotypes and the tumor microenvironment to account for the various aspects of relevant cancer biology, interdisciplinary teams reviewed each hallmark area and nominated a wide range of high-priority targets (74 in total) that could be modified to improve patient outcomes. For these targets, corresponding low-toxicity therapeutic approaches were then suggested; many of which were phytochemicals. Proposed actions on each target and all of the approaches were further reviewed for known effects on other hallmark areas and the tumor microenvironment. Potential contrary or procarcinogenic effects were found for 3.9% of the relationships between targets and hallmarks, and mixed evidence of complementary and contrary relationships was found for 7.1%. Approximately 67% of

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### Conflict of Interest Statement

Keith Block is an owner of the Block Center for Integrative Cancer Treatment and of North Shore Nutraceuticals; Charlotte Gyllenhaal is an employee of the Block Center for Integrative Cancer Treatment; Jack Arbiser is the inventor of US Patents involving derivatives of honokiol and NADPH oxidase inhibitors. He has also cofounded ABBY Therapeutics for the development of NADPH oxidase inhibitors; Penny Block is the Executive Director of the Block Center for Integrative Cancer Treatment and President of North Shore Nutraceuticals; Ralph J. DeBerardinis is a member of the scientific advisory boards for Peloton Therapeutics and Agios Pharmaceuticals; Anna Mae E. Diehl has grants from Shire-Research, Metabolon, and Gilead. She is also a consultant for Astrazeneca, Genentech, Japan Tobacco, and the NuSI Foundation; Byoung S. Kwon holds patents for methods regarding anti-CD 137 and adaptive CTL therapeutics; Valter D. Longo has an equity interest in L-Nutra, a company that develops medical food; Kapil Mehta is a scientific advisor to Lifecare Innovations, and holds India Patent 8.765.797, TG2 inhibitors and uses thereof; Michael P. Murphy holds intellectual property in mitochondrial therapies and has ownership shares in a company called Antipodean Pharmaceuticals Inc. which is trying to commercialize some of these compounds; Jeffrey C. Rathmell received indirect compensation from Novartis while working on this project; Luigi Ricciardiello received an unrestricted research grant from SLA Pharma AG, Switzerland.; John Stagg has a sponsored research agreement with Medimmune LLC and is on the scientific advisory board of Surface Oncology; Matthew G. Vander Heiden is a consultant, scientific advisory board member, and owns equity in Agios Pharmaceuticals

the relationships revealed potentially complementary effects, and the remainder had no known relationship. Among the approaches, 1.1% had contrary, 2.8% had mixed and 62.1% had complementary relationships. These results suggest that a broad-spectrum approach should be feasible from a safety standpoint. This novel approach has potential to help us address disease relapse, which is a substantial and longstanding problem, so a proposed agenda for future research is offered.

## Keywords

Multi-targeted; cancer hallmarks; phytochemicals; targeted therapy; integrative medicine

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## 1. Introduction

Cancer is a source of significant and growing mortality worldwide, with an increase to 19.3 million new cancer cases per year projected for 2025. More than half of cancer cases and mortality occur in low- and middle-income countries, and these proportions are expected to increase by 2025 [1]. Current treatments for cancer include surgery, radiotherapy and systemic treatments comprising cytotoxic chemotherapy, hormonal therapy, immunotherapy, and targeted therapies [2]. Cancer continues to stymie clinical treatment efforts, however, and the search for effective therapies continues.

This capstone paper describes the methods and results of a substantial effort by a large international group of biochemical and medical researchers, operating under the name of “The Halifax Project,” sponsored by a non-profit organization, Getting To Know Cancer. It summarizes and draws together material from a series of reviews on the hallmarks of cancer, presented in this special issue of *Seminars in Cancer Biology*, to present a conceptual framework for a new approach to cancer prevention and therapeutics. This approach involves the targeting of many specific high-priority anticancer mechanisms and pathways within a more comprehensive model of treatment and care. We refer to this as a “broad-spectrum” approach (i.e., an approach aimed at a broad spectrum of important mechanisms and pathways) [3]. The broad-spectrum approach involves combinations of multiple low-toxicity agents that can collectively impact many pathways that are known to be important for genesis and spread of cancer. By making extensive use of chemicals from plants and foods that have already been studied or utilized for cancer prevention and treatment, this approach offers a compelling rationale for addressing the underlying biology of cancer while being efficacious, non-toxic and cost-effective. We come together in the belief that a broad-spectrum approach of this type, in the context of a therapeutic environment including conventional treatment and attentive to optimal health, would provide genuine benefit in clinical outcomes for cancer patients. In this paper we describe the rationale for broad-spectrum therapeutics, detail the methods of the Halifax Project, summarize potential targets and agents related to eleven hallmark features of cancer, propose a research model for the development of broad-spectrum therapies, and call for action to advance this research model.

## 1.1 Rationale for Broad-Spectrum Approach

Primary motivations for the development of a broad-spectrum approach stem from the distinct limitations that are evident in many current targeted therapies and the personalized medicine paradigm. Molecular target therapies represent a significant advance in the treatment of cancer. They include drugs such as imatinib, an inhibitor of the tyrosine kinase enzyme BCR-ABL, which has made chronic myelogenous leukemia a more manageable disease, and inhibitors of vascular endothelial growth factor receptor (VEGFR), such as sunitinib, sorafenib and bevacizumab, used in renal and colon cancers [2]. Other important treatments based on tumor-specific targets are now in use, including examples such as epidermal growth factor receptor (EGFR) inhibitors (gefitinib, erlotinib) used in lung cancer, and the Her2 inhibitor trastuzumab used in breast cancer. Another approach is the synthetic lethal model [4] exemplified by research on poly ADP ribose polymerase (PARP) inhibition, in which mutational loss of one or more redundant components of a cell survival pathway in tumorigenic cells confers selective sensitivity to drugs that target remaining pathway components.

These drugs target cells bearing one, or at most a few mutated gene products or other abnormalities not found on normal cells. In the therapeutic context, the action of the targeted agents can efficiently address malignant cells, without some of the effects on normal cells notorious in cytotoxic chemotherapy. This enables therapeutic responses and remissions. Over time, however, the genetic heterogeneity of tumors increases, engendering resistance to treatment. Resistant cells drive the emergence of increasingly aggressive disease, through clonal expansion and clonal evolution [Figure 1]. Epigenetic modifications, heritable cellular changes not caused by alterations to DNA sequences, but by alterations such as methylation of DNA or modification of the histone protein associated with DNA, may also affect patterns of gene expression and drive cancers [5]. Relapses often occur after only a few months, and tumors reappear, sometimes in exactly the same areas in which they originated [6]. Moreover, targeted agents are not without serious side effects, such as treatment-related mortality with bevacizumab and cardiopulmonary arrest with cetuximab. Meta-analysis of trials of recently approved cancer drugs including targeted therapies versus older drugs showed increased rates of grades 3 and 4 toxicity (OR=1.52), treatment discontinuation (OR=1.33) and toxic deaths (OR = 1.40) [7]. This worsening of adverse effects has gone in large part unacknowledged.

The efficacy shown to date with targeted therapies, aside from now-established treatments such as bevacizumab and trastuzumab, is nevertheless still limited. Sunitinib, for instance, extends overall survival by 4.6 months in renal cancer, compared with the previous treatment of interferon- $\alpha$  [8]. While statistically significant, this degree of improvement is small comfort to afflicted patients, and challenges the extraordinary monetary investment in drug development as well as costs to the medical system that targeted therapies represent. The MOSCATO 01 trial of molecular triage was able to treat 25 of 111 patients with a variety of advanced cancers using therapies targeted to genomic alterations assessed from tumor biopsies [9]. Of these, 5 patients (20%) experienced partial response and 56% had stable disease. Based on the entire population of 111 patients, this is a partial response of less than 5%, suggesting limited efficacy to date, an outcome also seen in some other studies. [10]. On

a more hopeful note however, a combination of pertuzumab with trastuzumab and the chemotherapy agent docetaxel was recently found to extend overall survival among the subset of breast cancer patients whose tumors express Her-2 by 15.7 months [11].

Interestingly, harnessing the body's immune response against the tumor can also result in impressive durable clinical responses, perhaps because the immune system is a paragon of adaptability and can deal with changes in the mutational landscape of cancer to prevent escape from the therapeutic effect. Immunomodulatory antibodies recently licensed in the United states include ipilimumab as well as nivolumab and pembrolizumab, neutralizing two different inhibitory pathways that block antitumor T cell responses. These agents have achieved some successes in treating late stage cancers refractory to essentially any other treatments [12]. But even with these agents, response rates are still low and predicting who will respond is an unsolved challenge [13,14].

Many of these therapies are somewhat narrowly described as "personalized" because patients' tumors must be tested for specific mutations to stratify patients to the correct therapy. Viewed in the larger context of individual biological variation, of course, specific mutations drive only the smallest degree of personalization. Truly personalized treatment approaches can be seen to include a much more comprehensive assessment of genetic and even lifestyle factors, such as nutritional, biobehavioral (stress management) strategies, and exercise habits, along with other host variables such as inflammation and immune status. Such an approach to personalizing treatment can be found in the systematic practice of integrative medicine, which played a significant role in the development of this model of broad-spectrum cancer therapy. Some definitions of integrative medicine stress simply the inclusion of complementary and alternative therapies alongside orthodox treatment [15]. A more relevant definition emphasizes a patient-centered, multi-intervention treatment paradigm that addresses the full range of physical, mental, emotional and environmental influences, utilizing an array of disciplines including diet, mind-body and physical activity therapies in addition to conventional therapies and dietary supplements to support optimal health [16], based on laboratory testing that enables comprehensive personalization.

The stratification of patients for these targeted and personalized therapies poses practical challenges. As indicated earlier, over 50% of the increase in cancer incidence by 2025 is projected to occur in the developing world [1]. As industrialization develops in lower-income countries, occupational cancers are expected to increase, potentially aggravating this situation [17]. Cancer treatment in many of these countries is already becoming a social-economic challenge due to the expense and medical infrastructure required [18], and the new generation of treatments may further strain local resources. Currently, the platforms used for testing to personalize regimens include whole exome or whole genome sequencing, whole transcriptome sequencing, and comparative genomic hybridization with still others in development. It is likely that such tests, and related expense, will proliferate in the future. Managing treatment toxicity is also a taxing and complex problem, as these toxicities necessitate additional medical interventions.

The expense of the new targeted therapies is also concerning. Eleven of twelve drugs approved by the US Food and Drug Administration (US FDA) in 2012 were priced above

\$100,000 US per year per patient – perhaps not surprisingly in view of the accelerating costs of drug development [19]. Clinicians have drawn attention to these high costs: in 2013 more than 100 experts in chronic myeloid leukemia coauthored a paper calling for lower prices and broader access to these drugs [20]. The excessive costs have resulted in drugs not being approved for use by national or regional governments where cost-benefit analyses figure in approval processes [21]. While costs are expected to decrease after expiration of patents on the drugs, the costs for treatment in low- or middle-income countries may continue to be problematic. The potential for unsupportable financial stress on health systems challenges the research community to explore other treatment models that can be more sustainable in the face of the worldwide increase in cancer incidence.

The broad-spectrum approach that we describe here is primarily intended to address the two major issues of therapeutic resistance and cost. It is based on many of the insights of genomic sequencing in cancers. We now know that cancers harbor significant genetic heterogeneity, even within a single patient [6]. Based on this heterogeneity, cancers routinely evolve resistance to treatment through switching from one growth pathway to another [22]. The proposed strategy employs the basic principles of rational drug design, but aims to stem cancer growth by precisely targeting many growth pathways simultaneously. Some effort is now being made in combining targeted agents so that more than one pathway can be affected, but lack of therapeutic success, significant toxicity and costs make this a challenge [23–26].

We see the broad-spectrum approach as one that is complementary to existing therapies, preferably within the context of a genuinely integrative clinical system. Clinical situations in which such an approach might prove useful include (a) as a follow-up maintenance plan to conventional adjuvant treatment; (b) in situations of rare cancers and disease stages for which no accepted treatments exist; (c) for patients who do not tolerate conventional chemotherapy, hormonal therapy or targeted therapies; (d) for patients who experience relapse or progression after targeted treatment; (e) in hospice or palliative care patients where low- or non-invasive strategies are a legitimate and humane option; and (f) in situations in which high-cost agents cannot be obtained. Because of continuous heterogeneity among cancer cells, and their propensity for genomic instability, even a broad-spectrum approach is unlikely to cause complete remission. However, the design of this approach posed a substantial theoretical challenge, for which we chose to use the hallmarks of cancer as a broad organizing framework.

## 1.2 Hallmarks of cancer as a framework for developing broad-spectrum therapeutics

Douglas Hanahan and Robert A. Weinberg first published their concept of the hallmarks of cancer in 2000 [27]. The hallmarks “constitute an organizing principle that provides a logical framework for understanding the remarkable diversity of neoplastic diseases.” This framework encompasses the biological capabilities that cells acquire during the development of cancers that allow them to become malignancies as we know them. Six hallmarks were proposed in the 2000 publication: sustained proliferative signaling, evading growth suppressors, activating invasion and metastasis, enabling replicative immortality, inducing angiogenesis and resisting cell death. The concept of the hallmarks became widely

recognized and influential. In 2011, Hanahan and Weinberg expanded on the initial hallmarks to include other areas of cancer biology that they felt were equally important [28]. They pointed out two enabling characteristics critical to the ability of cells to acquire the six hallmarks, and two new hallmark capabilities. They also singled out the crucial nature of the complex tumor microenvironment in the appearance of the cancer phenotype. The enabling characteristics are genomic instability and tumor-promoting inflammation; the new hallmarks are deregulating cellular energetics and avoiding immune destruction.

The hallmarks framework helps to define domains in which high priority targets can be identified for therapeutic targeting. Hanahan and Weinberg point out that agents are in development that target each of the hallmarks. They also note, however, that in response to targeted therapy, cancers may reduce their reliance on a particular hallmark capability, such as angiogenesis, and instead heighten the activity of another capability, such as invasion and metastasis [29]. This reaction has been clinically verified in the case of glioblastoma [30].

Another model, which was proposed by Vogelstein et al. in 2013 [6], also attempts to describe the mechanisms and pathways that are relevant to many cancers. In this model, “driver” genes that drive cancer growth are distinguished from “passenger” mutations found in cancer cells that impart no growth advantage. Twelve major signaling pathways that drive cancer growth have been elucidated, including signal transducers and activators of transcription (STAT), Notch, DNA damage control and 9 others. These pathways are classified into three cellular processes underlying tumor growth: cell survival, cell fate and genome maintenance. Individual patients with the same cancer can have mutations on different pathways, leading to inter-patient heterogeneity. Yet within each patient there is also substantial heterogeneity, both within each patient’s primary tumor, and among and within metastases, with significance for treatment strategies. For instance, the smallest metastases visible through medical imaging may already have thousands of cells that harbor mutations rendering them resistant to current drugs [31].

Cancer mutations, moreover, are not simply a series of isolated targets. Beneath the surface of the cancer genome is a notably complex cellular signaling network, filled with redundancies. The elucidation of rational therapeutic combinations requires dynamic mechanistic models that reach beyond simple targeting [32]. What propels growth, dissemination and thus ineffective treatment and drug resistance actually appears not to be pathways acting in isolation but interconnected, multidirectional and dynamic networks [33]. Even sorafenib, which inhibits multiple kinases, is susceptible to the rapid development of resistance deriving from crosstalk in pathways such as phosphatidylinositide 3-kinase/protein kinase B (PI3K/Akt) and Janus kinase (JAK)-STAT, hypoxia-induced signaling or the epithelial-to-mesenchymal transition (EMT) [34]. Conventional drug discovery programs are now contemplating systems biology approaches aimed at furthering the network approach to pharmacology. The interdependence of cytokines, chemokines, growth factors, transcription factors, and their resulting proteomes, together with their relevance to cancer prevention and treatment [35], makes systems biology approaches most attractive [36]. This realization makes the significance of a broad-spectrum approach to cancer of even greater importance.

Clinicians as well as researchers recognize the importance of heterogeneity in cancer. At least one clinical center recognizes the significance of this heterogeneity, and intervenes with broad-spectrum approaches to respond to it. In a 2009 book, *Life Over Cancer*, based on a clinic in operation since 1980, K.I. Block lays out a model of nutraceutical-based targeting of nine “pathways of progression” and six metabolic factors impacting the challenges faced by all cancer patients [3]. The nine growth pathways are proliferation, apoptosis, treatment resistance, immune evasion, angiogenesis, metastasis, cell-to-cell communication, differentiation and immortality. Multiple targeting of these pathways with natural products is used to simultaneously address multiple interconnected growth pathways. Comprehensive molecular profiling maps patients’ growth pathways and provides for relevant natural product intervention. The six metabolic “terrain factors” are oxidation, inflammation, glycemia, blood coagulation, immunity and stress chemistry. Terrain-focused interventions are tailored to patients’ laboratory test results, which are monitored regularly to guide therapeutic modification. Interventions include elimination of maladaptive lifestyle patterns, adjusting exercise habits, improving diet, implementing biobehavioral strategies to diminish adverse consequences of unabated stress/distress, and using natural products and medications that affect specific targets such as C-reactive protein (CRP) [37], interleukin-6 (IL-6), nuclear factor  $\kappa$ -beta (NF- $\kappa$ B) [38], prostaglandin E2 and leukotriene B4 [39] for inflammation. Clinical observations and literature review suggest potential efficacy for this system in breast cancer (including a near-doubling of survival time of breast cancer patients in integrative care) and potentially other cancers [40,41]. Essentially, Block’ s clinical model systematically addresses multiple targets and pathways through a specific and selective broad-spectrum approach to treatment. While this system was developed in clinical practice, quite independently from the discussion of hallmarks and enabling characteristics by Hanahan and Weinberg, the conceptual overlap is obvious. That these concepts have already been used in clinical treatment provides powerful support for the viability of a carefully designed broad-spectrum approach.

The model we propose to use to develop a sound framework for a broad-spectrum approach recognizes these broad areas of conceptual overlap and agreement, and can be considered to best align with the hallmarks of cancer framework [27]. Our framework encompasses the molecular and metabolic diversity of malignancy recognized in Hanahan and Weinberg’ s hallmarks, Vogelstein’ s 12 growth pathways, Block’ s pathways of progression and terrain factors, and other emerging research. For the purposes of this project, we treat the 6 hallmarks, 2 enabling characteristics, 2 emerging hallmarks, and the tumor microenvironment equally as hallmarks of malignancy. From a design standpoint, each of these individual areas encompasses an important aspect of cancer’ s biology, so each was seen as important to consider for a therapeutic approach aimed at a wide range of high priority targets.

In mid-2012, the framework for this project and approach were shared with Douglas Hanahan. He later independently provided support for this type of approach in a paper, “Rethinking the war on cancer” [42]. Using a military metaphor, he suggests a three-dimensional cancer “battlespace” plan that attacks cancer in a full-scale war rather than individually targeted skirmishes. The first dimension is disruption of cancer’ s many capabilities, specifically those figuring in the hallmarks. Rather than just removing one

capability, as targeted therapies do, he explains that an ideal approach should target all the hallmark capabilities. The second dimension is defense against cancer's armed forces, implying specific targeting of the accessory cell types in the tumor microenvironment, such as tumor-promoting inflammatory cells. The third dimension represents the multiple battlefields of cancer: primary tumor, tumor microenvironment, lymph and blood vessels through which tumors disseminate, draining lymph nodes and distant organs. This dimension suggests still more targets.

A rapidly developing sub-discipline in oncology is the application of genetic and immune analysis of tumor tissue and the concomitant use of personalized therapies and prescriptions. These analyses allow better stratification of patients to treatments and clinical decision-making [43]. In the case of breast cancer alone, tests range from Her-2 testing, the basis of trastuzumab treatment to sophisticated suites of tests that analyze dozens of genes. These complex analyses assist in treatment decisions based on correlations with clinical outcomes by predicting treatment response, risk of recurrence and outcome. They suggest the size of the network of genes that affect just one cancer, and emphasize the significance of a broad-spectrum attack. Clinical utility of these tests is still under review [44].

Despite impressive progress in genomic and gene expression profiling, however, it is often impossible to fully characterize the range of immortalized cell variants within any given cancer. The perspectives offered by Hanahan Vogelstein and Block, as well as by the recognition of the network aspects of signaling pathways, however, suggest a larger number of targets may need to be reached. So the 138 driver genes, together with the 12 signaling pathways that comprise them, in addition to the molecular contributors to the hallmarks, and Block's nine pathways of progression and six terrain factors, help us delineate some of the most significant targets that should be taken into account in development of a broad-spectrum approach.

## 2. Methods

The effort to develop the concept of broad-spectrum targeting of cancer through a complex combination of agents, emphasizing naturally occurring chemicals, was developed by a non-profit organization, Getting To Know Cancer, and implemented within an initiative called "The Halifax Project." The aim of the project was to produce a series of reviews of the cancer hallmarks that could collectively assess and prioritize the many target choices that exist, and also identify non-toxic chemicals (primarily from plants or foods) that could safely be combined to produce an optimized broad-spectrum approach that has both prophylactic and therapeutic potential. To that end, it was envisioned that eleven teams of researchers would produce reviews on the ten cancer hallmarks plus the tumor microenvironment, which was treated as a hallmark for the purposes of this project. Each review was to describe the hallmark, its systemic and cellular dysfunctions, and its relationships to other hallmarks. A priority list of relevant therapeutic targets and corresponding approaches suited to those targets was requested, along with a discussion of research needed in the context of goals of the project. Natural compounds were emphasized because of the growing body of literature that supports the low toxicity and interesting potential that many of these substances have demonstrated (i.e., as targeted therapeutics or in

cancer prevention), while recognizing the variable effectiveness of these compounds in human trials as well as the undocumented safety or frank toxicity concerns with many natural products [45].

In recognition of the network of signaling pathways involved not only in drug resistance but the interconnection and maintenance of all the hallmarks, the project implemented a cross-validation step in the evaluation of targets and approaches. Because of the diversity of the targets involved in the 11 hallmark areas, it is not unreasonable to suspect that inhibiting or stimulating a target relevant to one hallmark may have an adverse growth effect or clinically adverse effect on a target in another hallmark. For instance, reducing DNA damage is a potential target for counteracting genomic instability. Activation of the immune system can counter DNA damage by eliminating damaged cells. However, activation of the immune system, while reducing overall levels of DNA damage, can contribute to chronic inflammation. [46].

Similar considerations apply to therapeutic approaches. For instance, triptolide, a component of the Chinese herb *Tripterygium wilfordii*, is known to cause apoptosis in cancer cells [47]. Extracts of the herb have been used in clinical trials for a variety of inflammatory and immune-linked conditions, and have demonstrated both antiinflammatory and immune suppressant activity, raising concern for its effect on immune evasion [48,49].

To address this issue, a specially designated cross-validation team was created within the project to evaluate all selected targets and approaches, i.e., to determine whether the inhibition or activation of targets, and the application of approaches, would have negative effects on other hallmarks. Each potential target-hallmark or approach-hallmark interaction was assessed to determine whether the pair had a complementary interaction (i.e., the interaction of the target or approach with the hallmark facilitated anticancer activity), a contrary interaction (i.e., the interaction of the target or approach with the hallmark had a potential adverse tumor-stimulating or tumor-progression effect), a controversial interaction (i.e., mixed indications of anticancer and tumor-stimulating effects), or no known relationship. A sample cross-validation table for dysregulated metabolism approaches can be accessed as Supplemental Table S1.

It is important to note that the cross-validation team was not given any restrictions for literature selection for this effort, and contributing authors were not restricted to cancer-related research. This approach was taken because it was realized at the outset that this breadth and specificity of knowledge does not yet exist in the literature. As a result, the types and sources of data gathered in this effort varied considerably, although original studies were consistently favored over review articles. Moreover, many studies that were cited in this effort considered only a compound's ability to instigate or promote an action that mimics a hallmark phenotype in a manner directionally consistent with changes that have been associated with cancer. So while we refer to these as anticancer or tumor-stimulating, the specificity of these activities and their implications for cancer treatment cannot and should not be immediately inferred from this database. In other words, the results from this aspect of the project were only compiled to serve as a starting point for future research, rather than a conclusive guide to therapy.

Targets or approaches that have a substantial number of “contrary” assessments are less attractive for inclusion in the broad-spectrum approach. On the other hand, the use of targets and approaches that appear to have the potential for multiple complementary interactions is consistent with principles of rational drug design, and akin to efforts to design “dirty” drugs (a pharmacological term for drugs with multiple targets – as opposed to single targets -- aimed at multidimensional conditions) [50]. Further evaluation of such “dirty” targets and approaches could be undertaken through more specific application of network pharmacology, for which new tools are currently becoming available [51]. The tabulated results, which appear in the individual reviews, are discussed in a later section of this paper.

The review teams needed for the Halifax Project were formed by first circulating an email to a large number of cancer researchers, seeking expressions of their interest in participation. The email was circulated in July 2012 by Getting To Know Cancer, and scientists were encouraged to submit their details on a dedicated webpage that offered additional project detail. From the pool of 703 cancer scientists who responded to the email, 11 team leaders were selected to each lead a group in producing a review of each hallmark, and an additional leader selected for the cross-validation team. Those leaders were then asked to form their own teams (by drawing from the pool of researchers who expressed interest in the project, and from their own circles of collaborators). Ultimately, 12 teams were formed. Team members were each encouraged to engage a junior researcher as well. This led to fairly large teams but it allowed us to distribute the effort considerably. Team leaders all received project participation guidelines; extensive and ongoing communication from the project leader, Leroy Lowe; copies of the relevant papers of Hanahan and Weinberg; and copies of [Life Over Cancer](#) by Block [3] as an example of practical clinical implementation of the broad-spectrum approach. In addition to the 11 teams, two guest editors, Anupam Bishayee and Keith Block, were selected for this special issue of *Seminars in Cancer Biology* in which the team reviews are published.

The team leaders and other team members who were able to attend the project workshop met in Halifax, Nova Scotia in August 2013 to discuss the project. Drafts of hallmark team papers were submitted in advance, and summary presentations made at the meeting. Other subject matter presentations included presentations on research funding in the natural products area (Jeffrey D. White, Office of Cancer Complementary and Alternative Medicine, National Cancer Institute) and the concept of driver and passenger genes (Bert Vogelstein, Johns Hopkins). Presentations on integrative cancer therapeutics made at the meeting are summarized below (Keith Block, Penny Block, Block Center for Integrative Cancer Treatment). Group discussions were held to facilitate communication among teams and project staff, and to assist teams in exploring the requirements and rationale for selection of targets and approaches.

Each hallmark team contained the following specialists: a lead author with demonstrated expertise in the hallmark area; domain experts who produced the descriptive review; anticancer phytochemical specialists; oncologists; and support researchers. The cross-validation team conducted background literature searches on the submitted targets and compounds from each review team, verifying their activity in relation to the other hallmarks. Results of the cross-validation effort were tabulated and reviewed by the individual teams.

Ambiguous results and areas of disagreement were reconciled, and the tables were ultimately incorporated into each hallmark review.

## 2.1 Selection of targets and approaches

It was assumed from the outset that, in a translational project aimed at the development of a broad-spectrum approach, there would be a practical upper limit to the number of potential targets in any given cancer that could be targeted. So each hallmark team was asked to select and prioritize up to 10 relevant targets for their hallmark area, bearing in mind that each target would serve as a starting point for the identification of a suitable low-toxicity approach that might be used to reach that target. In theory, it was understood that this could lead to as many as 110 targets for the entire project, and since the teams were also asked to select one therapeutic approach for each target, a maximum of 110 potential therapeutic approaches might be selected.

An “approach” was defined in this project as (1) a technique that will cause the body to respond in a manner that will act on the target (e.g., fasting, exercise etc.), or (2) a procedure involving an entity that can act on the target (e.g., phytochemical, dietary modification, synthetic drug, vaccination with peptides, locally administered oncolytic virus etc). Teams were then asked to identify “favored” approaches with patient safety as a top priority (i.e., least likely to cause harm or side effects even in combination with many other approaches). In addition to safety, other practical considerations for choosing favored approaches were suggested as follows:

- Efficacy – Greatest potential to achieve the desired action on the intended target across the widest possible range of cancer types
- Cost – Less expensive is better, and by no means cost prohibitive
- Intellectual Property – Free of intellectual property constraints if at all possible.

Approaches that do not have patents, that cannot be patented, and/or those that have patents that are expired are to be given priority over those that have existing patents.

**2.1.1 Selection of targets**—Extensive discussion took place about the principles of target selection. Certainly targets that are unique to cancer cells and tumor microenvironments, and that are not known to cause side effects when inhibited pharmacologically, would be a primary consideration. Targets induced by viruses or known carcinogens that are of importance in therapy would also be examined. Consideration of the nature of mutations in the cancer genome and the role of epigenetic modification were also discussed.

It is understood that great effort has been made to sequence the cancer genome to identify the most common mutations seen in different cancers. It is also known that different driver mutations may give rise to variant tumor cells, and the number of driver mutations required is limited, with just 2–8 per patient, which could potentially be assessed through whole genome sequencing of individual cancer patients. However, questions arise about treatment, since most of the currently available drugs are not potent enough to target all susceptible

cells. Moreover, the toxicity of existing drugs, if administered in combination protocols, is severely limiting, even at the reduced dosages that may be possible when using multiple agents. A strong rationale supports focusing on low toxicity chemistry (e.g., such as that which has been demonstrated by many anticancer and chemopreventive phytochemicals as the foundation for a broad-spectrum approach. A number of phytochemicals enhance absorption of other natural products through such mechanisms as cytochrome P450 modification [52], which could also enhance the possibilities for low-toxicity treatment, i.e., by reducing dosages needed for effective treatment.

Many driver genes are actually tumor suppressor genes, and in these cases, it is the loss of the tumor suppressor gene that allows development of cancer. Drugs cannot target these missing genes. Rather they must target unopposed pathways, such as pathways that are active upstream from the missing suppressor gene. For instance, the tumor suppressor forkhead box 0 (FOX0) normally causes apoptosis. If FOX0 is inactivated in cancer, an unopposed pathway upstream from it is the PI3K/Akt1 signaling pathway, which could alternatively be targeted [53]. The mitogen-activated protein kinase/extracellular-signal regulated kinase/mitogen/extracellular signal-regulated kinase (MEK) pathway, however, can act as a substitute or compensatory pathway to PI3K/Akt1. So, in order to effectively shut down replication, it would seem necessary to address these pathways as well.

Cancer-related signaling pathways, including even those that become driver pathways, may be epigenetically modified prior to their genetic modification in cancer pathogenesis [54]. This suggests an emphasis on chemoprevention or treatment of very early cancers. Targeting may be more straightforward to achieve under these conditions, since it is easier to modulate wildtype pathways pharmacologically than to treat the consequences of the onset of widespread aneuploidy. In this case, the cancer phenotype may well precede the cancer genotype by years or more. Combining knowledge of genetic and epigenetic changes in a particular tumor may result in the targeting of key pathways with fewer agents and reduced cost.

A more general consideration is that both direct and indirect targets and approaches can be considered. Direct targets are those that are familiar to us from targeted therapies – oncogenes, tumor suppressor genes, signaling pathways. Indirect approaches, however, are also potentially useful. For instance, evasion of the immune system is a hallmark of cancer [27], and immunomodulatory targets and approaches are appropriate to support the capacities of immune cells to eliminate tumor cells. Immune regulators are, in a sense, inherently multi-targeted due to the complexity of the responses they induce [55]. However, immunity is frequently compromised in patients under treatment with cytotoxic chemotherapies, as well as in the post-surgical period. Immune system approaches that also support the capacity of patients to tolerate or recover from surgery or toxic therapies indirectly support the health of cancer patients [56]. The potency of the immune system is illustrated by findings that chemotherapy may enhance antitumor immunity if given in the correct sequence, and that cancer refractory to chemotherapy or immune modulation alone may become susceptible to both together [57].

**2.1.2 Selection of approaches**—The need for low-toxicity agents as constituents suggested that phytochemicals –especially those “pre-screened” in humans owing to their presence in foods or traditional medicines -- should be carefully considered during approach selection. Each hallmark team therefore included cancer researchers who had considerable experience working with phytochemicals. In considering phytochemicals and other low-toxicity agents for inclusion in a broad-spectrum approach, however, several limitations in the literature promptly become clear.

First, the level of evidence for the effects of natural products on particular hallmark targets varies widely. The status of laboratory studies and clinical trials on several well-known phytochemicals, e.g. resveratrol, epigallocatechin gallate (EGCG), curcumin, lycopene and others, was recently reviewed [58]. The pleiotropic nature of the effects of these agents on apoptosis and arrest of cell growth has been emphasized, and their potential use in association with chemotherapy drugs has been acknowledged. Novel strategies based on a strategic combination of phytochemicals with broad-spectrum action together with radiation or chemotherapy agents aimed at overcoming resistance to apoptosis and enhancing sensitivity to treatment are also currently being considered [59,60].

Second, considerable clinical experience with combinations of phytochemicals and other natural agents in treatment of cancer patients exists. Detailed knowledge of the pharmacological effects of combinations of phytochemicals, however, is limited. There is a large literature on herbal combinations used in traditional Chinese medicine in both the laboratory and clinic [61–63], but the quality of older clinical trials is generally low. Additionally, laboratory studies of herbal medicines often use concentrations far higher than are clinically achievable. Supra-physiological concentrations can produce artefactual or irrelevant mechanisms of action or cause toxicity. The limited bioavailability of major phytochemicals makes this especially concerning, although products with improved bioavailability are in development [64]. In general, phytochemical research merits rigorous attention if we hope to gain a more detailed understanding of how these compounds affect the cancer hallmarks. Basic research needs to be followed up with better-designed, statistically powered clinical trials, if we hope to fully realize the therapeutic potential of phytochemicals.

In addition to laboratory studies and clinical trials, approaches may be suggested by epidemiological studies and the observations of integrative medicine, which uses diet and lifestyle therapies to affect medical conditions including cancer. Observational studies of soy consumption, along with corroborating evidence from clinical studies, suggest that dietary consumption of soy foods consistent with levels in the Japanese diet (2–3 servings daily, containing 25–50 mg isoflavones) may be associated with reduced risk of breast cancer incidence and mortality [65]. However, findings from animal studies [66] of negative effects of the soy isoflavone genistein on breast cancer and its treatment suggest some caution and avoidance of simplistic recommendations.

At all levels of investigation, the multi-targeted nature of phytochemicals as well as the integrative therapies is notable. Many isolated phytochemicals and herbals may alter large numbers of targets through multifaceted effects on physiology and metabolism [67–69]. A

basic complication of these multi-targeted agents, however, is the lack of mechanistic understanding and scientific acceptance of the roles of synergistic or additive molecules in formulation. Although used by human populations for millennia, there remains a question of how to develop and assess multi-component natural product formulations that are suitable for large-scale production. Genome-wide screening for assessment of targeted effects and experimentation with formulation of some herbs typical of traditional Ayurvedic medicine have recently been attempted in Asian laboratories, and are examples of attempts to better understand effects of multi-component agents [70–72].

### 3. Hallmarks of cancer

In this section we provide brief summaries of each hallmark review included in this special issue of *Seminars in Cancer Biology*. Each summary includes the targets and approaches selected in the hallmark review. Tables summarizing the targets and approaches and discussion of the cross-validation results follow. In addition, a summary of the impacts of integrative therapies on cancer-related molecular targets follows the hallmark summary material.

The hallmark summaries are roughly sequenced to capture the acquired capabilities of most cancers (see Figure 2). The section begins with *genomic instability*, an enabling characteristic, followed by *sustained proliferative signaling* and *evasion of anti-growth signaling*, two hallmarks that ensure that proliferation is unabated in cancer cells. These are followed by *resistance to apoptosis* and *replicative immortality*, two layers of defense that are believed to be bypassed in all cancers. Then we discuss *dysregulated metabolism and tumor-promoting inflammation*, which signal an important self-reinforcing evolution in the tumor microenvironment. Sections on *angiogenesis* and *tissue invasion and metastasis* speak to disease progression. Finally the *tumor microenvironment* and *immune system evasion* summaries relate to the last lines of defense to be defeated in most cancers.

#### 3.1 Genomic instability

Genomic instability plays a critical role in cancer initiation and progression. It provides the means by which a cell or subset of cells acquire a selective advantage over neighboring cells, enabling outgrowth and dominance in the tissue microenvironment. In normal cells, the fidelity of the genome is protected at every stage of the cell cycle by checkpoints. In cancer, the presence of aneuploid cells indicates the failure of one or more of these checkpoints. The resulting genomic heterogeneity may offer the cancer “tissue” growth advantages under selective pressures, including hypoxia, immune- and therapy-related challenges. Understanding these checkpoints, and how they are bypassed in cancer cells, may provide opportunities for the development of rational combinatorial or broad-spectrum treatment strategies, including nutraceuticals such as resveratrol [73,74].

A cell, either transformed or normal, must pass through multiple checkpoints during the process of division. These checkpoints are operated by functional complexes of proteins that either enable the cell to pass through the checkpoint (e.g. proto- or oncogenes) or prevent the progression through the cell cycle (i.e. tumor suppressors). The abundance of these proteins, and their functionality, can be modified by genetic changes to their encoding sequences or

by non-genetic, or epigenetic, changes that regulate their abundance. Briefly, small changes to the genes that encode proto-oncogenes or tumor suppressors will positively or negatively impact the function of the gene products. These small changes can be induced by environmental and lifestyle factors, such as toxic substances, diet, and smoking, or they can be encoded in the individual at conception. In the case of DNA damage generated by the environment, it is important that the cell repairs the damage effectively. Dysfunction in the molecules that come together to recognize and respond to sites of damage is often associated with human cancer. Thus, an understanding of the genetic or epigenetic status of DNA repair genes, and of the nutraceuticals that may modulate them [75], provides an opportunity to predict, detect, prevent and treat a variety of human cancers.

Growing evidences show that vitamins, minerals, and other dietary factors have profound and protective effects against cancer cells, whether they are grown in the lab, in animals, or studied in human populations. We have identified five targets against genomic instability: (1) prevention of DNA damage; (2) enhancement of DNA repair; (3) targeting deficient DNA repair; (4) impairing centrosome clustering; and, (5) inhibition of telomerase activity. Vitamins D and B, selenium, carotenoids, PARP inhibitors, resveratrol, and isothiocyanates are priority approaches against genomic instability; these approaches may dampen other enabling characteristics of tumor cells, such as replicative immortality, evasion of anti-growth signaling, tumor promoting inflammation, and oncogenic metabolism [73,76–82].

### 3.2 Sustained proliferative signaling

Proliferation plays an important role in cancer development and progression, as manifested by altered expression and activity of proteins related to the cell cycle [83,84]. Constitutive activation of a large number of signal transduction pathways takes place in cancer; this also stimulates cell growth. Early in tumor development a fibrogenic response is often seen. Along with the development of a hypoxic environment [85,86], this favors the appearance and proliferation of cancer stem cells (CSCs). The survival strategies distinguishing CSCs from normal tissue stem cells involve lack of cellular differentiation and alterations in cell metabolism, such as higher antioxidant levels [83,84]. These alterations take place as cells adapt to the changing microenvironment in affected tissue, prior even to the appearance of tumors. A part of this adaptation embodies epigenetic and genetic alterations in gene expression [6,87] that also confer resistance to many cytotoxic treatments [88,89]. Thus, adaptive resistance is likely acquired early in the pathogenesis of many tumor types.

Once tumors appear, the continued selection of cells with sustained proliferative signaling further promotes tumor heterogeneity. This is accomplished by growth and metastasis, which may be supported by overproduction of appropriate hormones (in hormonally dependent cancers), by promoting angiogenesis, by undergoing EMT, by altering the balance between apoptosis, necrosis and autophagy, and by taking cues from surrounding stromal cells. A number of natural compounds (such as EGCG) have been found to inhibit one or more pathways that contribute to proliferation [90–92]. Many of these compounds are nontoxic at doses that inhibit tumor growth and/or prevent the appearance of tumor. However, one of the keys to their efficacy involves their earliest possible therapeutic application. This is because their efficacy is likely to be the greatest in target tissues prior to

the appearance of a tumor where cellular heterogeneity is the least. In addition, many of the steps in carcinogenesis prior to tumor appearance are epigenetic in nature, and are more easily targeted by existing compounds, most of which target wild type molecules. This approach limits adaptive resistance, since early intervention does not have to deal with the issues of aneuploidy, loss of heterozygosity in multiple tumor suppressor genes, and point mutations in oncogenes. The contribution of bioinformatics analyses will be important for identifying signaling pathways and molecular targets that may provide early diagnostic markers and/or critical targets for the development of new drugs or combinations that block tumor formation. Thus, early intervention in pathways and molecules that mediate sustained proliferative signaling will limit adaptive resistance because it targets cells in tissues that have limited genotypic and phenotypic heterogeneity.

Targets selected for sustained proliferative signaling are hypoxia-inducible factor-1 (HIF-1) signaling, NF- $\kappa$ B signaling, PI3K/Akt signaling, wingless-type mouse mammary tumor integration site (Wnt) ( $\beta$ -catenin) signaling, insulin-like growth factor receptor (IGF-1R) signaling, cell cycle [cyclin-dependent kinases (CDKs)/cyclins], androgen receptor signaling, and estrogen receptor signaling. Possible therapeutic approaches include curcumin, genistein and resveratrol.

### 3.3 Evasion of Anti-growth Signaling

Normal cells must acquire the ability to continuously proliferate in order to transform into malignant phenotypes. However, cells have internal programs (anti-growth signaling) to oppose limitless growth. In order to continue to proliferate, cancer cells must somehow evade many anti-growth signals. In general, anti-growth signaling is mediated by the activation of tumor suppressor genes. The Cancer Genome Atlas has compiled data encompassing all tumor types, which indicates that *p53* is the most frequently mutated tumor suppressor gene followed by *PTEN*, *APC*, *ATM*, *BRCA2*, *VHL*, *RB*, *CDKN2A*, *BRCA1* and *WT1*.

Retinoblastoma protein 1 (RB1) was the first identified tumor suppressor and deletion of this gene is frequently found in cancers [93]. In many cases, the loss of RB is due to defects in upstream signaling molecules such as inactivation of INK4. Loss of p16ink4a results in unopposed activation of CDK4/6, which phosphorylates the RB protein thereby activating E2F-mediated transcription of genes involved in entry into the cell cycle [94].

Another tumor suppressor frequently deleted due to chromosomal loss is p53 [95]. In fact, more than 50% of all tumors have loss of p53 tumor suppressive functions. Recently, mutant p53 has gained renewed attention due to the fact that along with the loss of tumor suppressive functions, mutant p53 gains oncogenic/tumor promoting functions [96].

Epigenetic silencing of tumor suppressor proteins, which includes DNA methylation, histone methylation and acetylation, is another mechanism through which tumor cells evade anti-growth signaling. Many tumor suppressor genes have been found to have promoter hypermethylation in cancers [97]. Finally, anti-growth signaling plays a major role in treatment response and drug development. For example, the patients with human papilloma

virus-positive oropharyngeal cancer mostly retain wild-type p53 and have better prognosis and survival.

Although genetic alterations are mostly irreversible, epigenetic repressions are potentially reversible and targets for drug development. At least three histone deacetylase inhibitors, belinostat, vorinostat and romidepsin, are currently approved by the US FDA for cancer treatment. Many natural compounds also target the restoration of tumor suppressors through modifying epigenetic changes [98–102]. Thus, approaches to activate anti-growth signaling will open another chapter for cancer prevention and therapy.

The prioritized targets for anti-growth signaling are RB, p53, phosphatase and tensin homolog (PTEN), Hippo, growth differentiation factor 15 (GDF15), AT-rich interactive domain 1A (ARID1A), Notch, IGF-1R and others. The approaches are inactivation of E2F by down regulation of pRb using CDK inhibitors, activation of p53 through up-regulation of wild-type p53, activation of PTEN to inhibit PI3K-AKT, activation of Hippo pathways by inhibiting Yes-associated protein/transcriptional enhancer activator domain (YAP/TEAD) activity, induction of GDF15 through p53 activation, activation of ARID1A, blocking Notch pathway, and inhibition of IGF-1R to restore tumor suppressor pathways. Suggested phytochemicals for these approaches are EGCG, luteolin, curcumin, genistein, resveratrol, withaferin A, and deguelin. Furthermore, while the evasion of anti-growth signaling is a critical hallmark of cancer, other hallmarks are similarly important and a more integrative approach is necessary to simultaneously target several hallmarks of cancer to combat this deadly disease.

### 3.4 Resistance to apoptosis

Apoptosis naturally removes aged and unhealthy cells from the body [103]. However, in cancer, cells lose their ability to undergo apoptosis leading to uncontrolled proliferation and multiplication. These malignant cells are often found to overexpress many of the proteins that play important roles in resisting the activation of the apoptotic cascade, and one of the major hallmarks of human cancers is the intrinsic or acquired resistance to apoptosis [104]. Evasion of apoptosis may contribute to tumor development, progression, and also to treatment resistance, since most of the currently available anticancer therapies including chemotherapy, radio- and immunotherapy primarily act by activating death/apoptotic pathways in cancer cells [105]. Hence, a better understanding of the molecular mechanisms underlying tumor resistance to apoptotic cell death is expected to provide the basis for a rational approach to develop molecular targeted therapies.

Apoptosis resistance is multi-factorial and emanates from the interactions of various molecules and signaling pathways at multiple levels. Several mechanisms exist allowing cells to escape programmed cell death. Among them is the overexpression of the anti-apoptotic molecules. B-cell lymphoma-2 (Bcl-2) family proteins play a critical role in the biology of apoptosis resistance. Robust agents against the Bcl-2 homology domain 3 proteins are in development and accelerating toward clinical application. Other cell death mechanisms such as autophagy and necrosis can also be highlighted and strategies against them exist, including the use of natural agent such as EGCG. The role of the chaperone protein heat shock protein 70 (Hsp70) in apoptosis resistance is important, and natural

agents may also address this. Various molecular mechanisms support resistance to apoptosis in different disease models such as glioblastoma, multiple myeloma and chronic lymphocytic leukemia. Epigenetic players, particularly the non-coding RNAs/ microRNAs, are also of importance. Novel targets can be pinpointed, such as ecto-nicotinamide dinucleotide disulfide thiol exchanger protein (ENOX) and nuclear export protein chromosomal regional maintenance protein 1(CRM1), along with specific strategies to overcome these important drug resistance promoters. Other targets include inhibition of Mcl-1, activation of tumor autophagy, activation of tumor necrosis, inhibition of Hsp90, inhibition of proteasomes, and inhibition of EGFR and Akt. Approaches to these targets include gossypol, UMI-77, EGCG, triptolide, PXD, selinexor, and inhibitors of EGFR and Akt. Collectively, the knowledge gained through greater understanding of the apoptosis resistance targets and specific strategies is anticipated to bring forward a broad form of therapy that could result in better treatment outcome in patients suffering from therapy-resistant cancers.

### 3.5 Replicative immortality

Replicative immortality, the ability to undergo continuous self-renewal, is necessary for propagation of normal germ cells, but is not a property of normal somatic cells. When acquired by somatic cells that have sustained genetic damage or instability, replicative immortality allows accumulation of sequential aberrations that confer autonomous growth, invasiveness, and therapeutic resistance [106]. As a result, several mechanisms have evolved to regulate replicative potential as a hedge against malignant progression [107]. Senescence, a viable growth arrest characterized by the inability of affected cells to resume proliferation in the presence of appropriate mitogenic factors, is a specific response to the gradual shortening of chromosomal end structures (telomeres) with each round of cell replication, and a more general response to oncogenic and genotoxic stresses. Senescence often involves convergent interdependent activation of tumor suppressors p53 and p16/pRB [108,109], but can still be induced, albeit with reduced sensitivity, when these suppressors are inactivated. Doses of conventional genotoxic drugs required to achieve cancer cell senescence are often much lower than doses required to achieve outright cell death [110]. Additional targeted therapies may induce senescence specifically in cancer cells by blocking cyclin-dependent kinase mediated inhibition of RB-family proteins [111], or by exploiting cancer cells' heightened requirements for maintenance of telomere length through the action of the enzyme telomerase [112]. Developing optimized and truly holistic cancer prevention and treatment regimens will likely incorporate strategies that target replicative immortality.

The chief advantage to be gained by the use of senescence-inducing therapeutic regimens is elimination of the tumor's repopulating ability with reduced collateral damage compared to conventional cytotoxic regimens. There are, however, certain questions and risks associated with this strategy that must be addressed before its clinical adoption. In the case of telomere and telomerase based strategies, replicative senescence may occur more readily in rapidly dividing cancer cells bearing short telomeres than in slowly dividing stem cells with comparatively longer telomeres, but telomere lengths in cancer cells may still be long enough to permit sufficient population doublings for invasion and metastases to occur [112]. Moreover, telomere dysfunction promotes the development of chromosomal instability,

which in turn can generate mutations that enable cells to become drug resistant and/or activate mechanisms based on alternative lengthening of telomeres for telomere maintenance and/or become more malignant [113]. High priority should therefore be given to further research into the determinants of senescence stability, as the implications of delayed cell cycle re-entry, permanent cytoplastosis, or eventual clearance may be profoundly different. Lower doses of genotoxic drugs needed to induce senescence may reduce collateral damage to critical normal cells, but allow establishment of dormancy and/or adaptive resistance by cancer cells. The microenvironmental and systemic effects of senescent cells also need further clarification, as factors secreted by senescent cells may promote tumorigenic changes in nearby cells. Conversely, since it is almost impossible to kill all the cells in malignant tumors even using the highest tolerated doses of chemotherapy, combined use of an agent that induces or enhances stable senescence in the cancer cells that manage to retain viability might additively or synergistically increase therapeutic efficacy.

A number of potential targets can be singled out for further research, including telomerase, human telomerase reverse transcriptase (hTERT), mammalian target of rapamycin (mTOR), CDK4/6, CDK 1/2/5/9, Akt and PI3K. Several approaches deserve further research, although the activity of the phytochemicals in particular is still far from clinical utility. These include imetelstat, genistein, perillyl alcohol, palbociclib, dinaciclib, curcumin and EGCG.

### 3.6 Dysregulated metabolism

Dysregulated metabolism is a hallmark of cancer in which many cancer cells show increased glucose uptake and produce lactate. This characteristic is often called the “Warburg effect” [114], but how and why cancer cells reprogram their metabolic state is not well understood. Recent research has focused on understanding the metabolic changes accompanying oncogenesis [27]. A new model of cancer metabolism positions metabolic rewiring in cancer as a coordinated process to support rapid cellular proliferation by tuning cellular energy production needs towards biosynthetic processes. Indeed, several metabolic shifts associated with cancer can be linked to cellular growth, which serve to support biosynthesis of lipids, proteins, nucleic acids required for tumor formation and survival [115].

In several cases, expression of oncogenes and/or loss of tumor suppressors lead directly to changes in metabolism, by expression, activity, or flux of key metabolic nodes. Several components of glucose and glutamine metabolism have emerged as important regulators of metabolism in cancer. In glucose metabolism, hexokinase 2 (HK2), 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) and pyruvate kinase isoform M2 (PKM2) all regulate glycolytic flux. Using a “kitchen sink” analogy for glycolysis, both HK2 and PFKFB3 are regulators of the faucet, and fill up the sink. Conversely, PKM2 regulates the drain. Cancer metabolism turns on the faucet and plugs the drain, which over-spills the glycolytic pathway and provides metabolites used as building blocks for cellular growth. Efforts are underway to identify therapeutic strategies to “turn off the faucet” or “unplug the drain” in glycolysis, limiting cellular growth in cancer. Recent studies have also determined that glutamine is used as a fuel (glutaminolysis) in proliferating cancer cells. Glutamine oxidation can provide carbon and nitrogen for growth, and therefore is an attractive therapeutic target in cancer. Additionally, mutations in genes encoding enzymes directly

involved in metabolic pathways have been associated with several types of cancer. Rather than acting as a bystander or facilitator of oncogenesis, aberrant metabolism now has a pro-oncogenic role and has led to the redefinition of some metabolites as ‘oncometabolites’ [116]. Indeed, these oncometabolites are powerful influencers of proliferation, and are also positioned as new therapeutic targets.

In principle, a broad-spectrum approach to target metabolic shifts in cancer is likely to be a promising therapeutic strategy. However, studies using this approach to target dysregulated metabolism in cancer are in their infancy. Lessons could be learned from other strategies to target mitochondria or to target metabolism in order to identify efficacious and safe therapies targeted at cancer metabolism; some drugs targeting metabolism are being re-purposed for their antitumorogenic effects. Several approaches could be mentioned, such as 3-bromopyruvate, 1-(4-pyridinyl)-3-(2-quinolinyl)-2-propen-1-one (PFK-15), 6-[(3-aminophenyl)methyl]-4,6-dihydro-4-methyl-2-(methylsulfinyl)-5H-thieno[2',3':4,5]pyrrolo[2,3-d]pyridazin-5-one (TEPP-46), dichloroacetate, hexachlorophene, bis-2-(5-phenylacet-amido-1,2,3-thiadiazol-2-yl)ethyl sulfide (BPTES) and 2,3-Dihydroxy-6-Methyl-7-(phenylMethyl)-4-propyl-1-naphthalenecarboxylic acid (FX11), but data for these must be regarded as extremely preliminary, and they lack sufficient justification to be included in therapy without further study. Most target proteins or pathways identified as having potential to manipulate cancer metabolism have not been directly tested in the context of other hallmarks. The emerging efficacy of physiological interventions that manipulate cancer outcomes, such as fasting, calorie restriction, or exercise, could influence cancer metabolism and other hallmarks of cancer [117]. Future studies directly testing the ability to manipulate dysregulated metabolism in cancer will be an important and exciting new area of cancer biology that has potential for treating a variety of cancers.

### 3.7 Tumor-promoting inflammation

Virchow first proposed the role of inflammation in cancer in 1863, while observing the presence of leukocytes in neoplasms, and empirical evidence has since underscored the importance of this linkage [118,119]. The inflammatory milieu promotes a cellular microenvironment that favors the expansion of genomic aberrations and the initiation of carcinogenesis [120]. Chronic inflammation is linked to various phases of tumorigenesis, such as cellular proliferation, transformation, apoptosis evasion, survival, invasion, angiogenesis and metastasis [121–123]. Inflammation is also known to contribute to carcinogenesis through the generation of reactive oxygen species (ROS) and reactive nitrogen species which can damage DNA at the site of the tumor [124]. Free radicals and aldehydes, produced during chronic inflammation, can also induce deleterious gene mutation and post-translational modifications of key cancer-related proteins [125].

In addition, chronic inflammation has an influence on immune system constituents that are directly linked with cancer progression. Under normal conditions, immune cells, including macrophages, granulocytes, mast cells, dendritic cells, innate lymphocytes, and natural killer (NK) cells serve as the front line of defense against pathogens. When tissue disruption occurs, macrophages and mast cells secrete matrix-remodeling proteins, cytokines and chemokines, which activate local stromal cells (e.g., fibroblasts, adipocytes, vascular cells)

to recruit circulating leukocytes into damaged tissue (acute inflammation), to eliminate pathogens [126]. However, when these processes are initiated in the tumor microenvironment, they are not resolved, which leads to chronic inflammation of the “damaged” (tumor) tissue. Thus, while acute inflammation normally supports and balances two opposing needs for the repair of damaged tissues (apoptosis and wound healing), chronic inflammation represents a loss of this balance and the resulting confluence of factors has deleterious implications for the immune system [127].

Accordingly, the relationship between tumor-promoting inflammation and cancer is important to consider. Macrophage migration inhibitory factor, cyclooxygenase-2 (COX-2), NF- $\kappa$ B, tumor necrosis factor alpha (TNF- $\alpha$ ), inducible nitric oxide synthase (iNOS), Akt, and chemokines are important antiinflammatory targets that might be suitable for a multi-pronged therapeutic approach to inflammation suppression. Additionally, curcumin, resveratrol, EGCG, genistein, lycopene, and anthocyanins are forms of low-cost chemistry with little to no toxicity that could be employed to reach these targets.

Future translational work should make use of promising agents such as these (combined as constituents within a multi-pronged antiinflammatory approach) bearing in mind that some of these targets impact the immune system and can increase the risks associated with infection. Bioavailability challenges are also a concern for a number of these agents but recent advances in delivery systems will help address this issue.

### 3.8 Angiogenesis

Angiogenesis, the expansion of an existing vasculature, is the main mechanism of blood vessel growth in adults, and is therefore essential for tumor development [128]. Tumor angiogenesis is switched on by changing the balance between angiogenic factors and inhibitors in favor of angiogenesis [129], a process induced by tumor hypoxia as the tumor grows beyond a size of approximately 1 mm<sup>3</sup> [128, 130]. At more advanced stages, progressive genomic instability in the tumor leads to mutations in pathways regulating the production of multiple angiogenic factors [131], and stroma cells also become important sources of sustained angiogenic factor production [132]. These collectively result in a stronger and more complex angiogenic factor profile. It is therefore not surprising that targeted neutralization of a single angiogenic factor, which has been the focus for antiangiogenic cancer therapy so far, rarely produces long-term, antitumor effects [132].

Due to the multifactorial nature of tumor angiogenesis this process is likely to be more efficiently treated by targeting multiple aspects of tumor angiogenesis and vascular dysfunction at the same time. Ten of the most important targets for tumor angiogenesis and vascular dysfunction are to inhibit endothelial cell migration/tip cell formation, reduce structural abnormalities of tumor vessels, reduce hypoxia, inhibit lymphangiogenesis, reduce elevated interstitial fluid pressure, reverse poor perfusion, normalize disrupted circadian rhythms, suppress tumor-promoting inflammation, deactivate tumor-promoting fibroblasts and normalize tumor cell metabolism/acidosis.

Currently available non-specific antiangiogenic agents, able to perform some of these tasks, are however quite toxic, which renders them unsuitable for long-term use [131,133,134].

There is an urgent need to identify alternative compounds that could be used in combination over extended periods of time, targeting tumor angiogenesis broadly and thus lowering the risk of resistance. Plant-derived compounds, phytochemicals, are in many cases better tolerated than the synthetic analogues used in cancer therapy today. Furthermore, they often exhibit broader mechanisms of action and sometimes even higher affinity against important cancer targets compared to the synthetic alternatives [135]. Ten phytochemicals that may be effective as approaches to neutralize the 10 identified targets are oleanoic acid, tripterine, silibinin, curcumin, EGCG, kaempferol, melatonin, enterolactone, withaferin A and resveratrol. Further study is needed to determine the optimal use and combination of these phytochemicals in antiangiogenic therapy, focusing on delivery, toxicity and their use in prophylactic regimens.

### 3.9 Tissue invasion and metastasis

Cancer causes substantial patient morbidity and mortality globally, making it a key health issue. Metastatic dissemination of the disease to distant sites impacts prognosis, with metastatic diseases accounting for a vast percentage of cancer patient mortality [27,136,137]. Cancer cells must overcome particular obstacles in order to successfully disseminate to and establish at a secondary location, progressing through the metastatic cascade. Successful progression through this cascade is linked with numerous established changes in cellular functions leading to the acquisition of an invasive phenotype. This involves loss of cell-cell contact with the main tumor body, invasion, degradation and migration through surrounding tissue and extracellular matrix, secretion of angiogenic/lymphangiogenic factors and intravasation to the blood/lymph vessel, transport around the body and evasion of the immune system, extravasation at the secondary site and establishment of a secondary tumor [138,139].

Hence, factors influencing these processes such as cell adhesion molecules, proteolytic matrix degrading enzymes, cell motility and factors involved in the process of EMT have all been subject to scientific scrutiny. Additionally, the complex heterogeneity within tumors, together with cellular interactions between tumor cells and other, non-cancerous, cell types have been established to play key roles in metastatic dissemination and add further complexity to this cascade [137, 138]. While advances in the field of cancer research have been made, the process of cancer metastasis and the factors governing cancer spread and establishment at secondary locations are still poorly understood. Current treatment regimes for metastatic disease pose many adverse effects, which can further negatively impact on a subset of patients generally presenting with poorer health conditions. Hence there is a great need to develop new therapeutics that not only target tumor growth and inhibit metastasis but that also have a lower toxicity and reduced inherent side effects. Factors associated with metastasis such disruption of E-cadherin and tight junctions, key signaling pathways, including urokinase-type plasminogen activator, PI3K/AKT, focal adhesion kinase,  $\beta$ -catenin/zinc finger E-box-binding homeobox 1 and transforming growth factor (TGF)- $\beta$ , together with inactivation of activator protein 1 (AP-1) and suppression of matrix metalloproteinase-9 (MMP-9) activity should be considered as key research priorities.

The need can also be highlighted for new, low toxicity compounds, which interfere with these processes but remain inexpensive alternatives that are readily available and free from intellectual property. Phytochemicals, or natural products, such as those from *Agaricus blazei*, *Albatrellus confluens*, *Cordyceps militaris*, *Ganoderma lucidum*, *Poria cocos* and *Silybum marianum*, together with diet-derived fatty acids gamma-linolenic acid and eicosapentaenoic acid and inhibitory compounds have potential to inhibit these key metastatic events. These potential targets and strategies thus present new therapeutic opportunities to both manage cancer metastasis as well as having holistic effects against many of the hallmarks of cancer.

### 3.10 Tissue interactions in the tumor microenvironment

Cancer arises in an *in vivo* tumor microenvironment. This microenvironment is a cause and consequence of tumorigenesis, and consists of cancer cells and host cells that co-evolve dynamically through indirect and direct cellular interactions, producing metabolites and secreting factors that affect cancer progression [140,141]. In turn, this environment regulates the ability of a cancer to grow and survive via multiscale effects on many biological programs including cellular proliferation, growth and metabolism, as well as angiogenesis and hypoxia, innate and adaptive immunity [142]. Specific biological programs could be, based on our most recent understanding, exploited as targets for the prevention and therapy of cancer, including: the inhibition of cholesterol synthesis and metabolites, ROS and hypoxia, macrophage activation and conversion, regulation of dendritic cells, regulation of angiogenesis, fibrosis inhibition, endoglin, and cytokine signaling. These programs emerge as examples of important potential nexuses in the regulation of tumorigenesis and the tumor microenvironment that can be targeted.

Potential targets include metabolic programs that may broadly influence many cell biology programs that impact tumorigenesis and the tumor microenvironment (cholesterol synthesis and metabolites, ROS and hypoxia), inflammation, innate and adaptive immunity-related programs (macrophage conversion, dendritic cell activation, immune signaling), host microenvironment associated cellular programs (fibrosis, angiogenesis), and cytokine-mediated regulatory programs (IL-6, endoglin, and JAK). We have particularly focused on identifying approaches for inhibiting these targets that included natural products that have been suggested to have significant anticancer activity. Some of these molecules may more generally influence tumorigenesis and the microenvironment (berberine), others more specifically target ROS (resveratrol, desoxyrhapontigenin), macrophage conversion (onionin A), indoleamine 2,3-dioxygenase (IDO) regulation of dendritic cells (EGCG), cholesterol synthesis (genistein), fibrosis (naringenin), inflammation and immune signaling (piperine) and JAK signaling (zerumbone). This approach will provide a starting point for examining synergies that might be anticipated in testing certain targets and/or mixtures of natural chemical constituents that may modulate the tumor microenvironment in the treatment and prevention of cancer.

### 3.11 Immune system evasion

Tumors evade immune attack by several mechanisms including generation of regulatory cells and their secretions, defective antigen presentation, induction of immune suppressive

mediators either by cancerous cells themselves or by those in the microenvironment, tolerance, immune deviation and apoptosis.

Current approaches to immune therapy include a) cellular targets, b) molecular targets, c) vaccination therapy, d) therapy by phytochemicals, e) adoptive T cell therapy and f) immunomodulatory antibodies. Of these anticancer agents, the most important are those that are targeted in nature and to lesser extent, those that are non-specific in nature. Targeting specific costimulatory molecules such as cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) [143] or programmed cell death protein (PD1/PD-L1) [144] is considered an important anticancer strategy. Also, anti-PD-1 antibodies are showing enormous therapeutic potential in advanced cancers. Targets that are considered appropriate for broad-spectrum, low-toxicity therapeutics are less specific and include enhancing Th1 responses, enhancing  $\gamma\delta$  T cells, activation of macrophages, inhibition of Treg lymphocytes, enhancing natural killer cell activity and induction of IL-12.

There are a number of important nonspecific anticancer agents that have been reported, including vaccination therapy, as well as nonspecific bacteria-based therapies [145], and phytochemicals [146–148]. Phytochemicals (the biologically active components of fruits and vegetables) have been shown to exert protective effects against cancer. Examples of potential phytochemical approaches include extracts of *Ganoderma lucidum*, *Trametes versicolor*, *Astragalus membranaceus*, and *Lentinus edodes*, as well as astaxanthin and the polyphenol resveratrol analogue HS-1793. There is, however, a downside to phytochemical therapy such as their poor absorption by humans and rapid metabolism and excretion. More work is required to assess which phytochemicals block evasion of immune surveillance and also to determine which phytochemicals promote antitumor responses in cancer patients before these can be recognized for therapeutic value in the clinic.

#### 4 Summary of findings on targets and approaches in hallmark reviews

As described above, a cross-validation process was employed to review the proposed actions on each target and all of the approaches for known effects on other hallmark areas and the tumor microenvironment. Anticarcinogenic synergies and confounding/procarcinogenic effects were then compiled and summarized in Tables 1–3. Supplemental table S1, a sample cross-validation table for dysregulated metabolism approaches, was used in construction of Tables 2 and 3. Supplemental tables S2 and S3 contain the aggregated cross-validation tables from each review (with references omitted). More detailed discussion of these interactions can be found in the individual hallmark reviews.

Table 1 shows an alphabetical listing of prioritized targets from each hallmark review, as well as the number of contrary, controversial, none known and complementary interactions with all other hallmarks. Dysregulated metabolism targets do not appear in the table; too little is known about the targets in this new area of research to reliably assess their interactions with other hallmarks. Of these relationships, 3.98% were contrary, 7.62% were controversial, 21.74% of interaction assessments found no known relationship, and 66.71% were complementary.

Table 2 shows the prioritized therapeutic approaches – the phytochemicals, plant extracts and drugs chosen as modifiers of the priority targets. Of these, 1.08% were contrary, 7.62% were controversial, 34.05% had no known relationships and 62.1% were complementary. Both contrary and controversial interactions indicate potential conflict among the targets and approaches selected for different hallmarks that could result in a broad-spectrum approach with antagonistic, rather than synergistic effects.

The small number of contrary and controversial interactions is encouraging, and suggests that the potential for negative interactions among the selected targets and approach may be limited. However, this may also reflect the common bias in the literature to publish positive antitumor effects. Nearly a third of potential interactions were listed as having no known relationship, suggesting the need for substantially more research in this area. The large number of complementary interactions is also encouraging but may result from indirect or bystander effects.

Table 3, in which the different types of interactions of both targets and approaches are listed for each hallmark, reflects different levels of knowledge regarding hallmarks, as well as varying prevalence of complementary approaches. Genomic instability has the largest number of unknown relationships with the targets and approaches. On the other hand, tumor microenvironment, tissue invasion and metastasis and resistance to apoptosis have the highest number of complementary interactions for both targets and approaches. Small numbers of contrary interactions were found for the different hallmarks for both hallmarks and approaches, but the number of targets for replicative immortality and angiogenesis, reflecting mixed positive and negative interactions, were larger than for other hallmarks.

There are a number of limitations that should be noted in this delineation of cross-hallmark relationships. First, the researchers who assembled these results were not asked to distinguish between direct effects on other hallmark areas and reported effects on other hallmark areas that may have resulted in an indirect or “bystander” effect mediated through a different mechanism. In many cases, but not all, this distinction was made. Therefore it is likely that some of the complementary interactions do not represent a fully independent cross-hallmark relationship, but rather are simply indicative of some sort of downstream effect (e.g., within a signaling cascade or via some other signaling molecule that exerts pleiotropic effects). However, we did not feel that this project needed to investigate the nature of these complementary interactions in detail, especially since the clinical impacts of these interactions would be similar for indirect and direct effects. Instead, our main concern was focused on the possibility that a large number of cross-hallmark relationships might be revealed where actions with procarcinogenic or tumor-promoting potential had been reported. It was more important to identify contrary and controversial cross-hallmark interactions than complementary ones, since targets or approaches that exert procarcinogenic actions would normally need to be more carefully assessed (or avoided altogether) in the development of combination approaches or interventions.

The second limitation of these reports of cross-hallmark relationships is related to data quality. In some instances, the available evidence used to support the indication of a cross-hallmark relationships was robust, consisting of multiple studies involving detailed *in vitro*

and *in vivo* findings. In other instances, however, the underlying evidence that was used to report the existence of a cross-hallmark relationship was quite weak (e.g., consisting of only a single *in vitro* study involving a single cell-type). Again, the overarching goal in this project was to create a foundation that would allow us to look systematically across the literature in each of these areas, to help us shape the selection of the targets and approaches in order to comprehensively counter tumor growth pathways. So although we realized that not all of these reports of cross-hallmark relationships represented the same level of evidence, we still wanted to examine available evidence to flag targets and approaches where procarcinogenic actions had been reported.

There was also considerable debate within the task force over the value of tables containing only a simplified indication of a relationship (i.e., + or –) supported by evidence that varied considerably in quality. But since many individual studies and reviews that focus on therapeutic approaches fail to work systematically across the spectrum of incidental actions that might result from combining therapies, it was our opinion that a tabularized framework was the only way to ensure that we had assembled a complete view of cross-hallmark activity.

The types of approaches selected differed among different review teams. While some review teams selected all or mostly phytochemicals or plant extracts, some teams felt that the evidence for these was insufficient, and emphasized other types of molecules, including drugs in development. These may pose more difficulties for translational investigators due to intellectual property, toxicity or other concerns, but may offer advantages in a more clear understanding of their mechanisms. We suggest, however, that the approaches as well as the targets presented in Tables 1 and 2 can be viewed as simply a model for broad-spectrum cancer therapies, rather than as a final list. Some of the recommended approaches are clearly experimental, and further research will likely discover compounds, phytochemical or synthetic, that are not on this list that may be useful in a broad-spectrum approach. The prevalence of interactions where no interactions were found – over 20% for targets and over 30% for approaches – also suggests caution and a need for further research investigating potential cross-hallmark relationships as well as other mechanisms that may lead to toxicities.

Bioavailability of the phytochemicals chosen will also be a concern for future studies. The need for development of better preclinical models for screening compounds and testing rationally designed combinatorial therapies composed of compounds from any source is also obvious, and should clearly be a first step in the development of the broad-spectrum approach.

### 4.3 Role of integrative therapies in the broad-spectrum approach

Integrative medicine is an approach to health and healing that “makes use of all appropriate therapeutic approaches, healthcare professionals and disciplines to achieve optimal health and healing” [149]. A comprehensive integrative medicine intervention for cancer patients typically includes nutrition education, mind-body medicine and physical activity components, as well as dietary supplements including herbs, nutraceuticals and phytochemicals [3,150]. Such an intervention may contribute uniquely to a broad-spectrum

therapeutic approach through its impact on a wide variety of relevant molecular targets and hallmarks. Hallmarks that may be particularly impacted include genomic instability, tumor-promoting inflammation, dysregulated metabolism and immune system evasion. Because of their susceptibility to manipulation by diet, exercise and supplementation, these may be characterized as metabolic hallmarks.

Nutrition has long been the primary focus of research on integrative interventions for cancer. The World Cancer Research Fund and the American Institute for Cancer Research find that diets high in fruits and vegetables substantially reduce risks of several cancers [151]. Cancer prevention diets are also suitable after a cancer diagnosis [152]. For example, colon cancer patients eating a Western diet after diagnosis were at higher risk for recurrence and mortality than those with healthy diets [153]. Breast cancer patients who followed low-fat diets were found to have lost weight and had lower recurrence risks, especially among patients with estrogen receptor-negative cancers [154]. Trials of diets enriched in whole grains, low-glycemic diets, and both low-fat diets and Mediterranean diets enriched in olive oil and almonds reduced levels of inflammation as measured by CRP [155–158]. Low fat diets, weight loss and supplements (anthocyanins and fish oil) have been observed in randomized trials to reduce cytokines and signaling molecules [159–162]. Mind-body interventions have emphasized immune targets, with findings of interventional trials including activation of T cells and lymphokine-activated killer cells and increased natural killer cell activity [163,164]. Exercise interventions have documented effects on survival, IGF-1, natural killer cell activity, and sex hormones [165–168]. While much work remains to be done on integrative interventions, preliminary data suggest that integrative medicine may significantly support a broad-spectrum approach to cancer therapy.

## 5 Proposed research model

The review process for this project has revealed many potential targets and approaches. The cross-validation activity suggests that only a small number of targets and approaches affect other hallmarks in contrary or controversial ways. Indeed the results suggest that the design of a broad-spectrum approach should in fact be feasible from a safety standpoint. Although considerable research will be needed, disease relapse is a substantial and longstanding problem, so this novel model definitely warrants further investigation.

### 5.3 *In vitro* research

An array of *in vitro* models is available for preliminary study of broad-spectrum formulas. One question is the suitability of receptor-based assays versus cell-based assays. While receptor-based assays may seem more suitable for targeted therapy research, examining the impacts of a putative agent on a molecule such as NF- $\kappa$ B, which is at the intersection of multiple signaling pathways related to inflammation, might be advised. Cultivated cell lines are valuable for preliminary screening of mixtures, but are, in most respects, limited in their predictive ability. Isolated cell lines from clinical samples are an alternative, and use of transformed cancer cells versus non-transformed lines should be discussed. Tissue and organ explants are another useful *in vitro* model.

Basic research on the properties of the natural product and other approaches selected in the reviews needs to continue. The pharmacology of mixtures and combinations of phytochemicals, bioavailability, dose optimization and synergy are among the areas in which research is needed for many phytochemicals [169,170]. However, multicomponent herbal therapies used in traditional and alternative medicine have not received detailed analysis. Network pharmacology could be a means of exploring these presumed synergisms, and efforts are being made to apply this approach to the complex herbal mixtures used in traditional Chinese medicine [171]. Studies on the pharmacokinetics of herbal extracts and phytochemicals, which often begin at the *in vitro* level, are also needed [172].

In sum, given the complexity that is immediately suggested when combinations of approaches are possible, we strongly recommend that well-coordinated, multi-faceted programs be pursued initially to ensure that the constituent approaches that are selected are well-characterized using *in vitro* models, and that delivery methods that are selected for *in vivo* work receive careful evaluation before animal research is undertaken.

#### 5.4 *In vivo* research

Multiple *in vivo* models for further study of broad-spectrum approaches are also available. Two obvious choices are animal tumor models and human tumor xenografts implanted in athymic mice. While human tumor xenografts have the advantage in predicting effects of agents on human cancer cells, animal tumors offer some interesting choices for chemoprevention studies, since several are induced by exposure to various chemicals. The rodent tumors are questionable, however, in their ability to predict human responses to antitumor therapy. Differences in immunity are one consideration, most obviously with athymic mice but also with other animals. Many other differences are known. Rodents and humans, for instance, differ significantly in their blood levels of soy isoflavones after these are administered through a variety of dietary and experimental routes [173]. Isoflavone levels in rodent blood 20 to 150 times those in humans after similar oral intake have been observed, raising questions about the suitability of animals for prediction of phytochemical effects in humans.

Additionally, as shown in different preclinical mouse models, immune and inflammatory responses to cancer differ in young and old individuals, and many cancer treatments are likely to be less effective at older ages. Combination treatment including immunotherapeutic approaches may be most suitable for older animals. Therefore, there is a strong argument for testing and optimizing combination treatments in suitable model systems before attempting to apply them to cancer patients. The US National Cancer Institute Mouse Models of Human Cancer Consortium [174] has tried to provide the scientific community with accurate, reproducible models of human cancers that can be used in translational and preclinical studies. Such improved models could be of great importance for developing combination treatment strategies. Companion animals, such as dogs and cats, which experience several tumors analogous to human cancers, can also act as comparative models for human tumors. [175].

## 5.5 Clinical trials

Keeping in mind that a broad-spectrum approach may be used not only by itself, but also as adjuvant therapy with conventional agents, there are numerous potential settings for clinical trials, either for proof of principle or therapeutic goals. Preliminary studies could include metabolomic studies to identify metabolites of dietary interventions, or the pharmacokinetics and pharmacodynamics of phytochemical agents. A variety of settings can be contemplated for clinical trials. One period during which a broad-spectrum approach may be particularly appropriate is the perioperative period. Murine data demonstrate that tumor growth accelerates after surgery; there are also numerous anecdotal reports regarding cancer patients in whom rapid growth of metastatic tumors has been noted after surgery [176–181]. Further, there is reasonable human evidence that colon or rectal resection results in significant increases in the plasma levels of numerous proangiogenic proteins after surgery [182–185]. This period is not generally used for chemotherapy administration because of fears of impaired wound healing, but the above findings provide the rationale and motivation for systemically administering selected anticancer agents perioperatively.

Several non-standard chemotherapy agents, including phytochemicals, have been administered perioperatively in small studies. [186–188]. These agents upregulate immune function via nonspecific mechanisms. A Phase I trial assessing the combination of EGCG and silibinin in colorectal cancer is underway, with both agents given orally before and after surgery. [189–191]. Such trials represent an innovative approach to clinical assessment of natural products that can be carried out within a restricted time.

Although clinical trials of phytochemicals and plant extracts in cancer are limited compared to those with conventional chemotherapy, they are by no means lacking. Russo et al. [58] review nearly 50 ongoing and completed trials of phytochemicals and extracts in cancer prevention and therapy, noting that even though clinical research is still limited, preliminary results are promising. Most of the 50 studies took place in the United States, and most included a single phytochemical or single-herb extract. Nearly 3000 controlled trials of Chinese traditional medicine, 90% concerning herbals, were reviewed by Li et al. [192]. Only 16% of traditional medicine trials in this review reported use of adequate methods of randomization, and only a very small percentage reported study blinding, although quality of studies improved through time. Most Chinese herbal formulas contain multiple herbs and are aimed at many targets.

The design and execution of clinical trials of natural chemicals from plants and foods, however, has been challenging worldwide. An herbal products extension of the Consolidated Standards of Reporting Trials (CONSORT) randomized trial reporting guideline has been published to help improve herbal trial reporting [193]. A review of published studies of *Panax ginseng*, which is common in Chinese formulas but has been studied globally for many conditions, found that only 48% of them reported CONSORT-suggested items, and only 39% reported items from the herbal products extension [194], although these study designs also improved over time.

## 5.6 Translational considerations

Assuming that translational research work will involve a substantial combination of therapeutic agents such as those proposed in Table 2 as a starting point, a first step would be the selection of specific targets and approaches for preliminary study. To achieve a truly broad-spectrum effect, one strategy might be to use small doses of every approach that lacks significant contrary interferences. While such a mixture might be made up and applied to cell lines, it could be questioned whether the concentrations that could be achieved in the cells would be physiologically relevant, especially given the low bioavailability of many phytochemicals. Most *in vitro* work on single phytochemicals, however, has actually been conducted at high concentrations that are not achievable in humans. The pharmacokinetics and pharmacodynamics of phytochemicals are complex and many are not yet well known, although progress is being made on some agents [195]. Another method to narrow the number of phytochemicals that need to be in an agent might be to select the phytochemicals that are most widely represented across hallmarks, such as curcumin and resveratrol, and analyze combinations of these agents. Some of the selected approaches, e.g. silibinin, appear to have favorable pharmacokinetics [196]. Other phytochemicals with favorable pharmacokinetics could also be considered for inclusion in a broad-spectrum agent, such as phenethyl isothiocyanate [197]. Research is also urgently needed on the question of the stability of phytochemicals as well as synthetic compounds in mixtures.

Alternative approaches to the question of bioavailability are being explored, especially with the polyphenols. One of the main issues with these compounds, which include quercetin, green tea catechins, curcumin and others, is ensuring that circulating doses of aglycones (one of the active forms of these molecules), are sufficient for activity. After oral supplementation of foodgrade molecules at doses safe for humans (200–500 mg/day), only conjugated forms are found in the bloodstream. As an example, quercetin is not found in the plasma as aglycone or as the parent glycosides: at the doses usually employed in intervention studies, it would be found exclusively as methyl, sulfate or glucuronic acid conjugates [198]. This observation discloses a paradox common to many biologically active phytochemicals: if free aglycones are absent *in vivo* after a dietary intake or supplementation with high doses, how can we explain the high biological activity of these molecules, largely described *in vitro*?

Two main hypotheses can be considered. First, conjugated forms of some flavonoids (e.g. quercetin) may be biologically active. Second, after cellular uptake, these metabolites may be de-conjugated, regenerating the free aglycones. To sustain these hypotheses, key issues need to be addressed, such as the efficacy of mechanisms of uptake of polyphenol metabolites and the substrate specificity of each metabolite, which is largely unknown. The use of pure compounds tested *in vitro* may shed light on these questions. Alternatively, pharmacological doses (2–4 g/day) administered orally [199] may saturate the metabolic pathways of conjugation [200]. Efforts are being made, however, to improve bioavailability of these agents, such as microspheres [201], liposomes [202] and nanoparticles [203]. An additional complication is that individuals may vary in their absorption, distribution, metabolism and elimination of phytochemicals, based in some instances on genetic variability [204], dietary habits [205] and potentially on intestinal microbiota [206].

Considerations of quality control are essential along the spectrum of research from *in vitro* studies to clinical trials. Good agricultural practice, correct botanical identification and good manufacturing practice are mandatory to prevent adulteration, contamination and toxicity [207]. The example of PC-SPES, a botanical cancer remedy that was found to contain indomethacin, warfarin and synthetic estrogens, leading to its withdrawal from the market in 2002 resulted in greater awareness of the need for a strict approach to quality control [208].

## 6 Implementation of broad-spectrum research agenda

A variety of practical considerations come into play in translating the proposed research model into a developmental program. These include regulatory considerations, intellectual property, clinical considerations and funding.

### 6.3 Regulatory considerations

Research on the broad-spectrum model must be undertaken with regulatory constraints in mind. Laws controlling herbal medicines, which would likely apply to the broad-spectrum approach, typically have regulatory paths for herbal or traditional medicine products that differ from those for prescription drugs. Regulations relevant to traditional Chinese herbal medicines, perhaps the closest model for the proposed broad-spectrum approach, are reviewed by Fan et al. [209]. A few examples of national regulations regarding herbal medicines, traditional medicines and natural product drugs follow.

The United States has perhaps the most challenging regulations for drug approval, and regulations for mixtures are particularly complex. Some multicomponent formulas, have nevertheless been tested in clinical trials in the US [210,211], but are still being sold only as dietary supplements, without labeling for use in malignancy. The designation of the Botanical Drugs category may offer opportunities to broad-spectrum agents. A recent court decision declaring natural products unpatentable under US law adds an interesting wrinkle to the regulatory framework [212]. In Canada, development as a high-risk Natural Health Product could be considered [213]. China has a variety of regulatory categories that could be used for multicomponent natural product therapeutics [214]. The relevance of Chinese regulations for multi-targeted drugs has been explored [215]. In the European Union, the Marketing Authorization scheme for conventional drugs would need to be used, rather than the Traditional Herbal Regulation Scheme [216], increasing the challenge for developmental research. In India it is likely that New Chemical Entity approval would be required [217], since use in cancer would likely be considered beyond traditional herbal medicine usage. Japan allows herbal medicines to be registered as prescription or over-the-counter drugs [209]; prescription licensing appears likely for an anticancer therapeutic. A variety of regulations exist in other countries, which are beyond the scope of this paper, and which would need to be explored individually. We expect that working under these strict regulations will be difficult, but we do not see it as impossible.

An additional regulatory consideration is the acceptability of the broad-spectrum approach to institutionally-based ethical review boards needed for clinical research. In institutions located in countries in which multi-component herbal formulas are typical of traditional medicine, ethical approval of such formulas is common, as suggested by the large numbers

of clinical studies on traditional Chinese herbal medicine [192] and Japanese Kampo medicine [218]. Trials with multi-component formulas and natural products have been conducted under other regulatory schemes as well. For instance, Phase I and Phase Ib studies of BZL101, an extract of *Scutellaria barbata* in metastatic breast cancer have been conducted in the United States [219,220]. A 4-herb combination originating in traditional Chinese medicine, PHY906, has been the subject of a Phase I trial as an adjunct to capecitabine in advanced pancreatic cancer, also in the United States [221]. In general, provision of sufficient preclinical and drug formulation information, review of prior clinical studies, and possession of appropriate approvals from national-level agencies will facilitate approval of study protocols.

#### 6.4 Intellectual property

Herbs and natural products in their native forms do not have intellectual property protection, which should help in developing a low-cost, broad-spectrum formulation. Specified extracts and individual phytochemicals may have intellectual property of various types. Researchers could pursue intellectual property protection for specific broad-spectrum therapeutics they develop, as well as licensing to a pharmaceutical company with sufficient resources to support development and testing of the agent. Herbal extracts of some complexity have received patent or trademark status, and have been granted drug approval even in the United States. Examples include a mixture of green tea polyphenols known as Polyphenon E and sold as a patented drug sinecatechins for genital warts [222], and crofelemer, an extract from the South American plant *Croton lechleri*, approved for HIV-induced diarrhea [223]. The complexities of natural product patenting are beyond the scope of this paper but are covered in depth elsewhere [224].

#### 6.5 Clinical considerations for a multi-component natural product therapeutic

Based on current clinical experience with natural products administered together with conventional drugs, one may anticipate potential concerns with broad-spectrum therapeutics that would be administered jointly with conventional therapies. A primary concern is the interactions between drugs and herbs or phytochemicals, including both pharmacokinetic and pharmacodynamic interactions [225]. This has been of special concern in oncology due to the life-threatening consequences of lowered blood levels of drugs, and the potential for severe side effects when blood levels of a drug are increased or actions of herbal products reinforce those of conventional agents. Antiplatelet activity is common in natural products [226], and may aggravate clinical consequences in patients with thrombocytopenia due to chemotherapy or other drugs [227]. Several other examples of negative interactions are known or suspected. St John's wort (used for depression), contains the strong cytochrome P<sub>450</sub> 3A4 inducer hyperforin, which is known to reduce blood levels of many drugs, including irinotecan [228]. Green tea, which is often taken in high doses by cancer patients, has potential interactions with sunitinib [229], with hepatotoxic drugs [230], and with bortezomib. On the other hand, positive interactions have been observed with green tea and erlotinib, a combination now in clinical trials [231]. Curcumin is one of several natural products that act as chemosensitizers and radiosensitizers for several tumors, while protecting normal tissues [232]. The ability of herbs and other natural products to relieve treatment-related side effects should not be overlooked [233,234].

Furthermore, many natural products possess antioxidant activity. The role of oxidation in cancer progression and treatment is controversial [235]. Oxidative stress is increased in late-stage disease [236], which suggests that suppression would be beneficial. Antioxidants may relieve some adverse treatment effects caused by the reactive oxygen species generated by many chemotherapy drugs, but data on this point are not conclusive [237,238]. Randomized trials of antioxidant supplements given with chemotherapy do not find evidence of reduced efficacy, but research with better study design and larger sample size should be conducted [239]. Additionally, some natural antioxidants, including the polyphenols, manifest pro-oxidant properties in cancer cells, due to interactions with metal ions, which contribute to anticancer effects [240]. This pro-oxidant effect has been hypothesized to underlie the broadly multi-targeted actions of polyphenols such as curcumin and EGCG [241]. However, activity of most chemotherapy drugs depends on generation of ROS which should not be abrogated. Additionally, some oxidative metabolites may act as signaling molecules with anticancer activity [242]. Further, intracellular antioxidants may contribute to drug resistance [243]. Our understanding of the interactions of antioxidants and cancer thus continues to develop [244]. Patients are often warned not to supplement with antioxidants during treatment.

## 6.6 Funding

Development of new clinical agents that could be approved by regulatory agencies is an expensive endeavor. A recent economic model of drug discovery and development in the United States used industry-appropriate assumptions to estimate that the fully capitalized cost of a typical new single-molecule drug developed is now approximately \$1.8 billion, 63% of which is attributable to clinical development (Phase I–III studies) [245]. The details of such estimates are beyond the scope of this paper, but the financial challenges are clear. It is our contention that a multi-component broad-spectrum therapeutic approach is needed to complement and balance the current drug discovery paradigm, which focuses on narrowly scoped approaches and singular molecular targets, including targeted therapies, immunotherapy, “one mouse-one patient” avatars that identify personalized therapeutic regimens by implanting patients’ tumors into mice [246] and a variety of other approaches. Such an approach could be expensive to develop, and could face similar costs for trials and approval. However, a broad-spectrum approach could be aimed at wide applicability among many cancer types and subtypes. Thus, initial investment could be more easily recovered than is the case with narrowly-focused target therapies, since it would have utility across a large group of patients. Whether the development of the broad-spectrum approach should be carried forward by governments, for-profit pharmaceutical companies or even non-profit pharmaceutical companies is an open question.

## 6.7 Importance for low- and middle-income countries

The possibility that a broad-spectrum approach could be developed that is both effective and inexpensive is an important consideration, especially in low- and middle-income countries. One of the cost components of drug development is the cost of target identification and validation. However, in the Halifax Project the strategic list of targets that has been developed has been drawn from the open literature, so individual laboratories or nations that

are interested in developing a multi-component therapeutic approach can use this information as a starting point (i.e., as a basis for rationally selecting an array of targets).

## 7 Summary and conclusions

In spite of the importance of targeted therapies now used in treatment and currently in development, it is clear that most cancers cannot be successfully addressed solely with single-target therapies. The history of cancer treatment has taught us the importance of drug resistance, stemming ultimately from genetic heterogeneity in cancers. Our therapeutic tool kit now includes a large array of cytotoxic chemotherapies, molecular target drugs, immunotherapies and hormonal therapies. A major paradigm in cancer research, in response to the advances in analysis of the cancer genome, is the development of increasingly targeted therapies. Examples illustrating the vigor of research and development in this area are several targeted therapies that have received approval in 2013–2014 by the US FDA, including ceritinib (anaplastic lymphoma kinase inhibitor), ramucirumab (VEGFR2 blocker), ibrutinib (Bruton's tyrosine kinase inhibitor), trametinib (MEK inhibitor) and dabrafenib (B-Raf inhibitor) [245].

At the same time there is an increasing awareness of a need to develop a therapeutic approach to address the genetic heterogeneity within tumors. Even within this group of newly approved agents, the combination of trametinib and dabrafenib was approved for joint use in 2014, due to the rapid (6–7 months) development of resistance to the sole use of B-Raf inhibitors. The emergence of the concept of multiple hallmarks of cancer [27], the nine pathways of progression [3] the listing of 138 driver genes [6] and the recognition of the importance of network pharmacology [51] all attest to the importance of this issue. A recent review similarly suggests combining antiinflammatory and antioxidant treatment in long-term maintenance therapy of cancer [248]. It is the contention of the Halifax Project that a broad-spectrum approach to cancer prophylaxis and treatment (i.e., simultaneously attacking many targets) is a strategic and promising response to our increasing understanding of the significance of genetic heterogeneity.

Although current drugs have notably increased initial responsiveness to treatment in comparison to traditional approaches to chemotherapy, there remain situations in which a broad-spectrum approach could make real contributions. Some examples include use as follow-up to conventional treatment; for rare cancers; for patients who do not tolerate conventional treatment; for early-stage disease, when aggressive treatment should be avoided; and in hospice and palliative care. If significant interactions with treatments can be avoided, it might even be possible to use such approaches in conjunction with targeted therapies and other treatments.

What are the implications of this broad-spectrum strategy for current clinical practice? First, clinicians should realize that this paper presents a developmental research program, not clinical guidelines. Use of uninformed selections of phytochemical or botanical extracts in poorly-defined clinical situations is unlikely to deliver positive results. Further, as noted above, concerns with interactions of natural products with conventional treatments should be kept in mind. That said, lifestyle therapies appear to affect multiple molecular targets and to

improve the health of cancer patients in a variety of ways, and integrative lifestyle modifications should be assessed as a health-promoting foundation for use of broad-spectrum therapeutics [3,150]. Clinical trials are now defining beneficial impacts of natural products [249]. The positive implications of dietary therapies for improvement of the metabolic hallmarks of inflammation, dysregulated metabolism, genomic instability and immune system evasion should be kept in mind [250,251]. Clinicians choosing to use natural product supplements should attend to product quality and be familiar with advances in the formulation of poorly absorbed polyphenols and other phytochemicals [201–203].

The development of the broad-spectrum approach is not without cost. A primary need is further development of preclinical models for testing of combinatorial therapies, including study of the stability, pharmacodynamics and pharmacokinetics of agents comprising multiple phytochemicals and other molecules. While some of the targets and approaches recommended in these reviews are well-known and have been the subject of multiple reviews, others are still only promising leads and may need much better characterization before being adopted as constituents in such an approach. For example, among approaches, curcumin, genistein, resveratrol and EGCG boast a wealth of fundamental research, whereas other approaches such as tripterine, oleanoic acid and withaferin A will require additional basic research. Targets are also in need of more basic research, especially in replicative immortality and in dysregulated metabolism, a field in which studies of relevant targets are just beginning. The approaches analyzed in these areas are similarly only in the most preliminary stages of research. All the hallmarks, however, include targets and approaches that need substantial basic research. Determining how many of the suggested targets should be included in a broad-spectrum approach is also a question that needs substantial research. Supporting these areas of basic research should be an initial goal of funding efforts.

The pharmacology of mixtures of natural products is another area in which basic research is most relevant to the goals of this project. There is certainly a body of research on complex mixtures of natural products [211,215,218,219,221]. A recent study suggested that EGCG lowers the concentration of curcumin needed to reduce proliferation and induce apoptosis in uterine leiomyosarcoma cells [252]. Traditional Chinese medicine formulas have also been subjected to extensive pharmacological testing [253,254]. However, much remains to be done in quantitative optimization of formulas as well as in selection of optimal natural product extracts or phytochemicals. And although this effort emphasized phytochemicals, it is also important and relevant to study defined botanical and food extracts. Standardized black raspberry extract, for instance, has produced positive results in human trials on apoptosis, angiogenesis and several specific targets selected in the project [255]. Aged garlic extract [256] increased immunity in advanced cancer patients, and lyophilized strawberries [257] improved premalignant esophageal lesions. Defined herbal extracts such as PHY 906 and BZL101 mentioned above have demonstrated preliminary clinical antitumor activity [220,221]. Stability and pharmacokinetic properties of complex mixtures are another critical research need, as are proper methods of quality control [258].

The development of complex natural product agents appears ripe for cross-disciplinary approaches as well as attention to the process of translational research. Natural products research, in fact, has long been nurtured most successfully in multidisciplinary and

collaborative working groups [259], and the teams that authored the reviews in this special issue were notably interdisciplinary themselves. In view of the challenges as well as the unique opportunities this new concept entails, scientists wishing to take part in the development of broad-spectrum approaches to cancer would do well to commit themselves to a set of new attitudes and skills. Laboratories and grant proposals have achieved success typically based on highly focused exploration of a small intellectual niche. The broad-spectrum approach upends this paradigm. Building linkages with laboratories across campus, or even with the department down the hall, is not always encouraged in academic institutions. But this challenge is not insurmountable, and institutions and granting agencies have successfully mounted efforts that embrace, for instance, natural product development “from the field to the clinic” [260,261]. At the same time, integrative oncology centers globally employ broad-spectrum clinical approaches involving therapies ranging from natural products to meditation in the service of patient needs [262]. There is thus no need to start from absolute zero in building the cross-disciplinary alliances we project will be needed for this effort.

What will be needed is a core group of scientists willing to become advocates for this approach. Advocacy must take place within academic institutions, as institutional silos, perhaps reluctantly, open their doors to collaboration. Institutional review boards and grant offices may need education in the concept of the broad-spectrum approach. Advocacy must take place at higher levels as well. National funding agencies and charitable foundations that currently support cancer research need to heed these recommendations and shift quickly to embrace the rationale for this interdisciplinary team-based approach. Grant review committees may need to confront established interests promoting competing studies with more familiar narrow aims. Creativity in funding initial research efforts will be needed. International agencies interested in addressing the growth of cancer in low to middle income countries might be convinced that broad-spectrum approaches could result in lower-cost and often more culturally acceptable therapeutic tools for these areas.

Now is the time to begin the work of advocating for broad-spectrum therapeutic approaches in cancer. Scientists need to seize the opportunities provided by the unique information provided in this special issue to expand their acquaintance with this model - and perhaps with the scientists themselves who are already involved in this effort. Scientists and clinicians alike should become advocates to their institutions, to funding sources and to the wider public. This dimension of cancer biology and therapy has too much potential to allow it to languish. At the same time, clinical challenges mount, despite the emergence of new targeted therapies. We look forward to seeing concentrated energy and intellect focused on this new approach, and to seeing it yield significant therapeutic benefits in the future.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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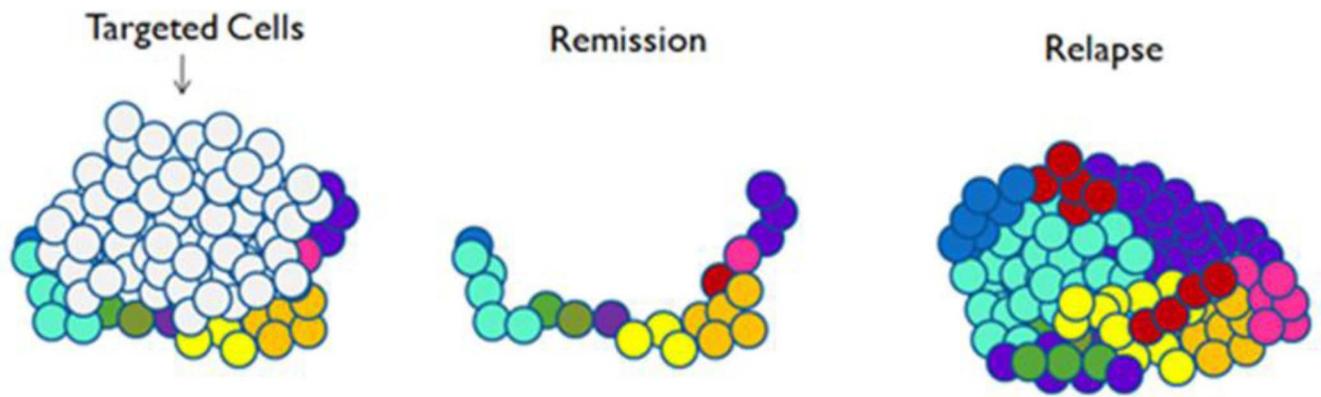
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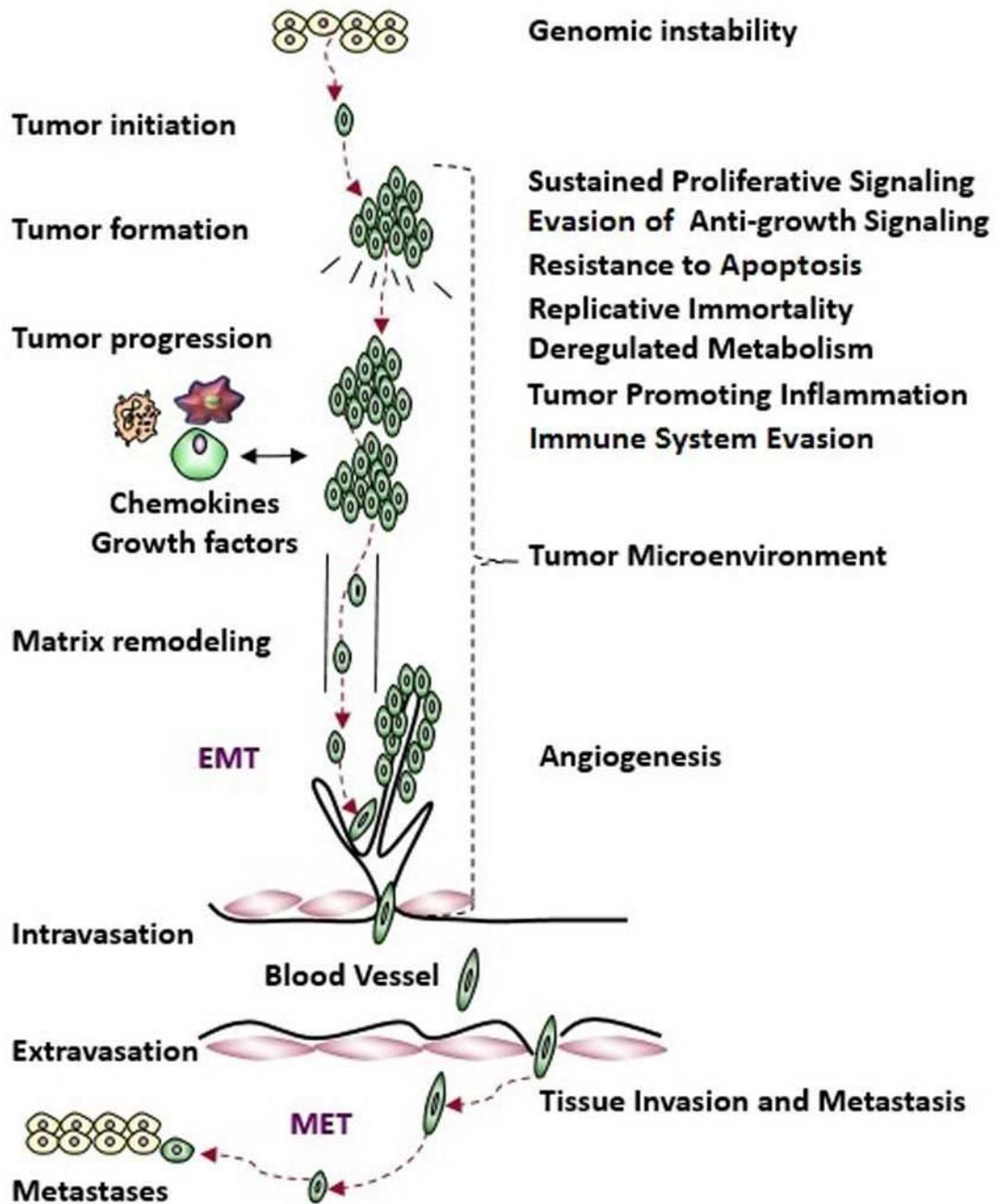
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**Figure 1.** Diagrammatic representation of removal of susceptible cells by a targeted cancer therapy resulting in disease remission, which leaves genetically heterogeneous resistant cells to proliferate, resulting in relapse.



**Figure 2.** Hallmarks of cancer, sequenced roughly in the order in which these capabilities are acquired by most cancers, as portrayed in the graphical representation of tumor evolution.

**Table 1**

Prioritized targets with summary of information from cross-validation tables.

Hallmark <sup>1,2</sup>	Target (action on target)	Contrary	Controversial	Complementary	None known
AP, RI, TPI	Akt (inhibit)	0	0	11	0
SPS	Androgen receptor signaling (suppress)	0	2	8	1
TIM	AP-1 (inhibit)	1 RI	0	7	3
EAG	ARID1A (activate)	1 TIM	0	5	5
AP	Bcl-2 (inhibit)	0	1	9	1
RI	CDK 1/2/5/9 (inhibit)	1 TME	0	9	1
RI	CDK 4/6 (inhibit)	1 GI	1	8	1
SPS	Cell cycle (CDKs/cyclins) (attenuate)	2 IS, TIM	0	9	0
GI	Centrosome clustering (block)	0	0	8	3
TME	Cholesterol metabolites (inhibit)	0	0	7	4
TME	Cholesterol synthesis (inhibit)	0	1	8	2
TPI	COX-2 (inhibit)	1 AN	0	10	0
TPI	CXC chemokine (inhibit)	0	3	5	3
AN	Disturbed circadian rhythms (normalize)	0	2	9	0
GI	DNA damage (prevent)	1 TPI	3	5	2
GI	DNA repair (enhance)	1 TPI	3	5	2
EAG, TIM	E-cadherin (restore)	1 AN	4	4	2
EAG	E2F (inactivate)	1 TME	0	7	3
AP	EGFR (inhibit)	0	0	10	1
AN	Elevated interstitial fluid pressure (reduce)	0	0	9	2
TME	Endoglin (inhibit)	0	1	5	5
AN	Endothelial cell migration/tip cell formation (inhibit)	0	0	7	4
AP	Enox (inhibit) (AP)	0	0	5	6
SPS	ER signaling (suppress)	1 TIM	3	7	0
EAG	ER stress (induce)	2 AN, TIM	1	7	1
TIM	FAK signaling (inhibit)	0	0	9	2

Hallmark <sup>1,2</sup>	Target (action on target)	Contrary	Controversial	Complementary	None known
TME	Fibrosis (inhibit)	0	0	6	5
EAG	Growth differentiation factor 15 (induce)	1 GI	0	5	5
SPS	HIF-1 signaling (inhibit)	0	0	9	2
AP	Hsp90 (inhibit) (AP)	1 TIM	0	8	2
RI	hTERT (inhibit)	0	1	8	2
AN	Hypoxia (reduce)	0	1	10	0
TME	IDO (inhibit)	0	1	7	3
EAG, SPS	IGF-1R (inhibit)	0	0	9	2
IE	IL-12 (induce)	1 AP	0	5	5
TME	IL-6 (inhibit)	0	3	7	1
TPI	iNOS (block)	1 AN	1	6	3
TME	JAK (inhibit)	0	0	10	1
AN	Lymphangiogenesis (impede)	0	1	4	6
TME	M2 macrophage conversion (inhibit)	0	0	7	4
IE	Macrophages (activate)	2 SPS, TIM	2	3	4
AP	Mcl-1 (inhibit)	0	0	10	1
TPI	MIF (block)	0	0	9	2
TIM	MMP-9 (suppress)	0	1	7	3
RI	mTOR (inhibit)	0	2	8	1
SPS, TIM, TPI	NF-KB signaling (inhibit)	0	2	8	1
IE	NK cell activity (promote)	0	0	7	4
EAG	NOTCH (block)	1 AN	0	8	2
AP	Nuclear exporter CRM1 (inhibit)	0	0	6	5
RI	PI3K (inhibit)	0	0	11	0
EAG, SPS, TIM	PI3K/Akt signaling (inhibit)	0	0	11	0
AN	Poor perfusion (improve)	0	1	7	3
AP	Proteasome (inhibit)	0	0	10	1
TME	ROS (inhibit)	0	2	7	2
AN	Structural abnormalities of vessel walls (inhibit)	0	0	7	4

Hallmark <sup>1,2</sup>	Target (action on target)	Contrary	Controversial	Complementary	None known
GI	Target deficient DNA repair	1 TPI	2	5	3
GI, RI	Telomerase (inhibit)	0	0	10	1
TIM	TGF- $\beta$ (inhibit)	1 RI	2	7	1
IE	Th1 response (promote)	1 TPI	0	5	5
TIM	Tight junctions (promote)	1 AN	0	6	4
TPI	TNF- $\alpha$ (block)	1 IE	1	8	1
IE	Treg lymphocytes (inhibit)	0	1	6	4
AP	Tumor autophagy (activate)	1 TPI	4	4	2
AN	Tumor cell metabolism/acidosis (normalize)	0	0	9	2
AP	Tumor necrosis (activate)	2 AN, TME	3	5	1
AN	Tumor-promoting fibro-blasts (deactivate)	0	0	9	2
AN	Tumor-promoting inflammation (suppress)	0	0	7	4
TIM	Urokinase plasminogen activator (suppress)	1 RI	0	7	3
TME	VEGF (inhibit)	0	3	8	0
EAG	Wildtype p53 (upregulate)	0	0	10	1
SPS	Wnt (B-catenin) (inhibit)	0	3	7	1
EAG	YAP/TEAD activity (inhibit)	0	0	6	5
TIM	$\beta$ -catenin/ZEB1 (inactivate)	0	0	7	4
IE	$\gamma\delta$ T-cell activity (promote)	2 TPI, AN	0	4	5
	<b>Totals:</b>	32	62	543	177
	<b>Percentages:</b>	3.93%	7.62%	66.71%	21.74%

<sup>1</sup>For each target, the following items are shown: the hallmark(s) for which it was selected, and the number of other hallmarks with which it has complementary relationships, contrary relationships, no known relationships and controversial relationships. For targets that have contrary relationships, the conflicted hallmark(s) are shown. Totals and percentages of each type of relationship are shown at the end of the table.

<sup>2</sup>AN = Angiogenesis, AP = Resistance to Apoptosis, DM = Dysregulated Metabolism, EAG = Evasion of Anti-Growth Signaling, GI = Genomic Instability, IE = Immune Evasion, RI = Replicative Immortality, SPS = Sustained Proliferative Signaling, TIM = Tissue Invasion and Metastasis, TME = Tumor Microenvironment, TPI = Tumor Promoting Inflammation.

**Table 2**

Prioritized approaches with summary of information from cross-validation tables.

Hallmarks <sup>1,2</sup>	Approaches	Contrary, Conflicted Hallmarks	Controversial	Complementary	None Known
DM	3-bromopyruvate *	0	0	7	4
TIM	5,6-dihydro-4H-pyrrolo[1,2-b]-pyrazoles *	0	0	2	9
TPI	Anthocyanins	0	0	9	2
IE	Astaxanthin	0	0	7	4
IE	<i>Astragalus membranaceus</i> polysaccharide	1 AN	0	6	4
TME	Berberine	1 IE	0	9	1
DM	BPTES *	0	0	5	6
GI	Carotenoids	0	1	10	0
TIM	Cordycepin	0	0	8	3
AN, EAG, RI, SPS, TME, TPI	Curcumin	0	0	11	0
EAG	Deguelin	0	0	7	4
TME	Desoxyrhapontigenin	0	0	2	9
DM	Dichloroacetate *	0	0	7	4
RI	Dinaciclib *	0	0	6	5
AN, AP, EAG, RI, TME, TPI	EGCG	0	0	11	0
TIM	Eicosapentaenoic acid	0	0	8	3
AN	Enterolactone	0	0	7	4
DM	FX11 *	1 GI	0	2	8
TIM	Gamma linolenic acid	0	0	7	4
TIM	Ganoderic acids	0	0	7	4
IE	<i>Ganoderma lucidum</i> polysaccharide	0	0	9	2
EAG, RI, SPS, TME, TPI	Genistein	0	5	6	0
AP	Gossypol	0	0	9	2
TIM	Grifolin	0	0	6	5

Hallmarks <sup>1,2</sup>	Approaches	Contrary, Conflicted Hallmarks	Controversial	Complementary	None Known
DM	GW5074 *	0	1	3	7
DM	Hexachlorophene *	0	0	6	5
IE	HS-1793 (polyphenol resveratrol analogue) *	0	0	5	6
RI	Imetelstat *	0	1	4	6
GI	Isothiocyanate	0	0	10	1
AN	Kaempferol	0	0	7	4
IE	<i>Lentinus edodes</i> polysaccharide	0	0	8	3
EAG	Luteolin	0	0	9	2
TPI	Lycopene	0	0	8	3
AN	Melatonin	0	0	10	1
DM	Metformin *	0	1	10	0
TME	Naringenin	0	2	6	3
AN	Oleanoic acid	0	0	10	1
TME	Onionin A	0	0	1	10
TIM	Pachymic acid	0	0	6	5
RI	Palbociclib *	1 TIM	0	4	6
GI	PARP inhibitor *	0	0	9	2
RI	Perillyl alcohol	0	0	10	1
TME	Piperine	1 IE	0	7	3
DM	PK15 *	0	0	6	5
TIM	Polysaccharide ( <i>G. lucidum</i> )	0	1	8	2
AN, DM, EAG, GI, SPS, TME, TPI	Resveratrol	0	2	9	0
GI	Selenium	1 TPI	2	6	2
AP	Selinexor *	0	0	3	8
AN, TIM	Silibinin	0	0	11	0
DM	TEPP-46 *	0	0	3	8
IE	<i>Trametes versicolor</i> polysaccharide-k	0	0	3	8

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Hallmarks <sup>1,2</sup>	Approaches	Contrary, Conflicted Hallmarks	Controversial	Complementary	None Known
AN	Tripterine	0	0	5	6
AP	Triptolide	1 IE	0	9	1
AP	UMI-77 *	0	0	5	6
GI	Vitamin B	0	2	3	6
GI	Vitamin D	0	0	10	1
AN, EAG	Withaferin A	0	0	9	2
TME	Zerumbone	0	0	6	5
TIM	$\beta$ -(1-6)-D-glucan ( <i>A. blazei</i> )	0	0	6	5
	<b>Totals:</b>	7	18	403	221
	<b>Percentages:</b>	1.08%	2.77%	62.10%	34.05%

<sup>1</sup> For each approach, the following items are shown: the hallmark(s) for which it was selected, and the number of other hallmarks with which it has complementary relationships, contrary relationships, no known relationships and controversial relationships. For approaches that have contrary relationships, the conflicted hallmark(s) are shown. Totals and percentages of each type of relationship are shown at the end of the table. Approaches are natural products except for those noted by asterisks.

<sup>2</sup> AN = Angiogenesis, AP = Resistance to Apoptosis, DM = Dysregulated Metabolism, EAG = Evasion of Anti-Growth Signaling, GI = Genomic Instability, IE = Immune Evasion, RI = Replicative Immortality, SPS = Sustained Proliferative Signaling, TIM = Tissue Invasion and Metastasis, TME = Tumor Microenvironment, TPI = Tumor Promoting Inflammation.

\* Targeted therapy, synthetic compound or natural product analog/derivative

**Table 3**

Numbers of targets and therapeutic approaches for each hallmark with the following relationships: complementary relationship, contrary relationship, no known relationship and controversial relationship. Based on cross-validation tables.

Type of relationship	Genomic Instability	Sustained Proliferative Signaling	Tumor-promoting Inflammation	Evasion of Anti-growth Signaling	Resistance to Apoptosis	Replicative Immortality	Deregulated Metabolism	Immune System Evasion	Angiogenesis	Tissue Invasion and Metastasis	Tumor Microenvironment
<b>Targets</b>											
Complementary	30	52	53	53	62	34	55	44	44	65	61
Contrary	2	1	6	0	1	0	0	2	9	5	3
None known	52	24	18	20	13	37	23	34	15	7	9
Controversial	1	5	6	7	4	12	5	4	12	3	7
<b>Therapeutic Approaches</b>											
Complementary	35	51	44	50	62	37	42	22	40	60	64
Contrary	0	0	1	0	0	0	0	3	2	1	0
None known	39	20	26	17	11	37	27	39	23	11	9
Controversial	1	8	5	5	1	1	6	12	7	0	0