Review

Therapeutic interventions in Cancer

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ABSTRACT

Cancer metabolism is a new and exciting field of biology that provides a novel approach to treating cancer. Cancer cell metabolism is marked by profound changes in nutrient requirements and usage to ensure cell proliferation and survival. In cancer, this metabolic reprogramming is coordinated with proliferative signaling and regulated by the same oncogenes and tumor suppressor genes to ensure efficient proliferation.

Glycolysis (sugar metabolism), fatty acid metabolism and autophagy (self metabolism) are three pathways shown to play a critical role in cancer metabolism. Identifying and disrupting certain enzymes in these and perhaps other, metabolic pathways provides a powerful intervention point for discovery and development of cancer therapeutics.

The therapeutic intervention in brain cancer and other cancers where IDH1 mutations are present using new drugs that can target the IDH1 metabolic pathway, while Agios Pharmaceuticals identified an exciting new biomarker, 2HG, that could be used to develop an important diagnostics that the mutated IDH1 gene has a novel enzyme activity consistent with a cancer-causing gene, or oncogene. This breakthrough discovery shows that the mutated form of IDH1 produces a metabolite, 2-hydroxyglutarate (2HG), which may contribute to the formation and malignant progression of gliomas, the most common type of brain cancers.

The nano-capsule technology holds enormous promise for the successful molecular targeting of CK2 specifically in tumor cells. Additionally, the data suggest that the s-50 TBG nano-capsule has the ability to target metastases, including bone metastases, which considerably raises its potential for advanced cancer therapy. The current advances on resveratrol, a grape-derived phytochemical with chemo-preventive potentials owing to its demonstrated activity to inhibit cancer cell proliferation, reactivates apoptosis, and additional properties that can allay growth of cancer.

Cancer bioinformatics is a critical and important part of the systems clinical medicine in cancer and the core tool and approach to carry out the investigations of cancer in systems clinical medicine and for the development of bioinformatics methods, network biomarkers and precision medicine.

The protein HSP90 is a target of promising anticancer drugs. An analysis of the components of HSP90 complexes in tumours reveals a path that may lead to predictive assay of drug sensitivity in cancer patients.

Keywords: Therapeutic intervention, Cancer, IDH1 mutations, CK2, HSP27, Micronuclei (MN) frequency, Resveratrol, Cancer Bioinformatics

1. INTRODUCTION

Till date, biotechnology has produced more than 200 new therapies and vaccines, including products to treat cancer, diabetes, HIV/AIDS, and autoimmune disorders. There are more than 400 biotech drug products and vaccines currently in clinical trials, targeting more than 200 diseases, including various cancers, Alzheimer’s disease, heart disease, diabetes, multiple sclerosis, AIDS, and arthritis, the importance of biotechnological methods and techniques, which are increasingly dominating the process of drug research and development [1].

An average approval of 10–15 products a year indicates
that pharmaceutical biotechnology is a highly active sector. Amongst these, the number of genuinely new biopharmaceuticals is around 40%, indicating the high innovative character of research; some of these products are likely to be future blockbusters. Examples are monoclonal antibody-based products such as Rituxan® (Rituxan®/MabThera®) for the treatment of cancer with $18 billion in sales in 2009, insulin and insulin analogues ($13.3 billion/2009), and finally erythropoietin-based products ($9.5 billion/2009) [2].

The global market is growing by 7% per year for protein-based therapeutics and among all blockbuster drugs only one is a classical low molecular drug, the other four top selling drugs are derived from the biotechnology sector [3]. In addition to new drug entities (NDE), biosimilars or follow-up-biologicals will continue to increase in market value. This trend is supported by new or adapted approved routes from the regulatory bodies such as the EMA (European Medicines Agency) and the FDA (Food and Drug Administration).

Established molecular biology techniques for protein engineering, such as phage display, construction of fusion proteins or synthetic gene design, have matured to the level where they can be transferred to industrial applications in recombinant protein design. Traditional engineering has focused on the protein backbone, while modern approaches take the complete molecule into account. In designing muteins, glycoengineering and post-translational modification with non-natural polymers such as polyethyleneglycol (PEG) have affected around 80% of approved protein therapeutics [1].

Humanized monoclonal antibodies represent a recent and very significant addition to the anticancer therapeutics. With improved therapeutic strategies due to these agents, however, there are also various, sometimes unexpected, side effects.

Most of the monoclonal antibodies used in oncology share a risk of infusion-related manifestations, including the possibility of anaphylaxis; these reactions usually appear early on during the first administration. Hematological toxicity is also frequent, especially if the antibodies are associated with chemotherapy; the resulting neutropenia - and with some agents lymphopenia - is associated with an increased risk of infection. Cardiac failure and pulmonary complications have been reported with some of these agents, especially in patients with prior cardiac or pulmonary co morbidities.

Many new techniques for improving the industrial effectiveness of pre-existing enzymes have been made possible since the discovery of PCR. These include DNA sequencing, site-directed mutagenesis and DNA shuffling.

The efficiency of antibodies can be addressed through the ability of binding to highly specific surface structures and a fairly uniform structure. Apart from vaccinations, antibodies were introduced early on in the therapy of neoplastic diseases and for the prevention of acute tissue rejection in patients with organ transplant. Muromonab CD3, with the trade name Orthoclone OKT3®, is an immunosuppressant monoclonal antibody that targets the CD3 receptor on the surface of T cells. As an adverse reaction, antimouse antibodies can be formed leading to reduced efficiency after repeated injection.

To improve tolerance, chimera between mouse and humans were designed. From the protein sequence of the established murine antibodies, the genetic code was deciphered and substituted in the conserved Fc region by the respective human genetic code. These antibodies are called chimeric, in contrast to humanized antibodies where the framework regions are also substituted. Examples are Daclizumab, Zenapax (humanized) [4], Abciximab in ReoPro® (chimeric) [5], and Rituximab in Mabthera® (chimeric) [6] as antineoplastic antibodies for non-Hodgkin lymphoma.

A dietary herbal supplement containing lignans and indole-3-carbinol may reduce the risk of breast cancer by reducing free estrogen levels; suggest results from a randomized control trial. [7]

The CAGTE, which represents green tea phytochemicals potentially available after upper gastrointestinal digestion, was found to be depleted in flavan-3-ols when compared to the pre-digested green tea extract. At high concentrations, CAGTE exhibited direct anti-proliferative effects, in line with the reputed anti-cancer properties of green tea polyphenols. [8]

Heat shock proteins HSP27, HSP70 and HSP90 are molecular chaperones whose expression is increased after many different types of stress. They have a protective function helping the cell to cope with lethal conditions. The cytoprotective function of HSPs is largely explained by their anti-apoptotic function most of them involving the activation of cystein proteases called caspases. Apoptosis and differentiation are physiological processes that share many common features, for instance, chromatin condensation and the activation of caspases are frequently observed [9].

The importance of CK2 as a target for cancer therapy, since the dual role of CK2 in cell proliferation and cell death it was proposed that CK2 could serve as a key target for cancer therapy. Protein kinase CK2, a protein serine/threonine kinase, plays a global role in activities related to cell growth, cell death, and cell survival. CK2 has a large number of potential substrates localized in diverse locations in the cell including, for example, NF-κB as an important downstream target of the kinase.

CK2 interacts with diverse pathways which illustrates the breadth of its impact on the cellular machinery of both cell growth and cell death giving it the status of a “master regulator” in the cell. With respect to cancer, CK2 has
been found to be dysregulated in all cancers examined demonstrating increased protein expression levels and nuclear localization in cancer cells compared with their normal counterparts. Janeen H. Trembly et al proposed CK2 as a potentially important target for cancer therapy.

The design of a tenascin based sub-50 nm (i.e., less than 50 nm size) nanocapsule in which an anti-CK2 therapeutic agent can be packaged is highly promising because this formulation can specifically deliver the cargo intracellular to the cancer cells in vivo. Thus, appropriate strategies to target CK2 especially by molecular approaches may lead to a highly feasible and effective approach to eradication of a given cancer.

Phytonutrients are most found in pungent vegetables (like onions and garlic), bitter ones (like mustard greens), or ones with acquired tastes like mushroom. The most potent were cruciferous vegetables (those in the cabbage family), specifically broccoli and its payload of glucoraphanin—the precursor of sulforaphane. Since traditional Asian diets include not just large helpings of soy but also generous pours of green tea, which contains cancer fighting epigallocatechins. Specialized diets are far from the only way to decrease chances of cancer, but they do add flexibility to cancer prevention strategies. Future dietary recommendations might also take genetics into account. The composition of the microbiota, such as with probiotics, should be tweaked to maximize the cancer-fighting effects of foods.

Cancer bioinformatics as an emerging strategy is one of the most critical and useful approaches to systems clinical medicine for clinical research and applications and improve the outcomes of patients with cancer. I.e. omics science, bioinformatics tools and data, clinical research, disease-specific biomarkers, dynamic networks, with precision medicine, together fighting cancer and improving the life quality of patients with cancer.

Micronuclei (MN) frequency in peripheral blood lymphocytes of cancer patients showed the evidence about a role of MN in various steps of carcinogenesis, the existing evidence about a role of MN in various steps of carcinogenesis and clearly shows that the level of baseline chromosome damage in untreated cancer patients is much higher than in cancer-free referents.

Indeed, MN is generally used as a biomarker of chromosomal damage, genome instability, and cancer risk, integrating acquired mutations and genetic susceptibility. Several factors could explain cancer predictivity of MN, e.g., environmental exposure to genotoxic agents, lifestyle factors, micronutrient deficiency, and genetic factors.

The drugs normalise blood vessel growth around tumours. Cancer blood vessels are normally leaky chaotic, by correcting this, angiogenesis inhibitors may turn the vessels into a more efficient pipeline for delivering chemotherapy. It has been noticed in some patients that when the disease does return after treatment aimed at angiogenesis, its more aggressive than in patients not treated with drugs, the effect of angiogenesis inhibiting drugs and of knocking out the gene encoding VEGF (vascular endothelial growth factor).

Acute myeloid leukaemia in humans can be caused by different genetic changes that translate to markedly different responses to standard therapies. Scott Lowe at cold spring harbor laboratory in New York and his colleagues created a mouse that closely resembles two common variants of the diseases. the team irradiated the animals to kill off blood cell precursors and then injected them with blood precursor cells that have been genetically modified to recapitulate one of the two types of leukemia. As in the human forms, one was very responsive to treatment, the other resisted common therapy. In addition to providing new insight, the mice may make for a good preclinical model for drug screening. [10]

2. CANCER THERAPEUTICS:

Human melanoma is resistant to treatment with retinoic acid, which is effective against several other cancers, but by activating the transcription factor SOX9, researchers at the national institute in Bethesda, Maryland, may have discovered a way to make retinoic acid effective after all. The SOX9 activity slows cell division and sensitizes melanoma cell to the drug. In mice injected with melanoma cells, a drug that activates SOX9 had mild effect on its own, but when combined with retinoic acid significantly reduces size of tumours. [11]

Oncologists use drugs that limit a tumour’s blood supply to prevent its growth. Although the initial effects of these drugs are beneficial to patients; new data suggest that their long-term effects warrant further study. Angiogenesis — the formation of new blood vessels — is a hallmark of cancer, and allows tumour growth. Anti-angiogenic therapy offers great promise and is often used to treat cancer, either alone or in combination with chemotherapy. But like all other cancer therapies, agents that inhibit tumour angiogenesis and prone to either intrinsic or acquired resistance. Paez ribes et al and Ebos et al showed in two preclinical (in vitro and animal) studies published in cancer cell that, depending on treatment conditions, anti angiogenic therapy could theoretically increase the likelihood of tumour invasiveness and spread. [12]

Berry extract inhibits growth and induces apoptosis of human breast cancer but not non-tumourgenic breast cells. The ripe purple berries of the native Indian plant Eugenia jambolana Lam., known as jamun are popularly consumed and available in the united states i Florida and Hawaii. Despite the growing body of the data on the chemopreventive potential of edible berry extracts, there is paucity of such data for jamun fruit.

A standardized jamun fruit extract (JFE) were studied for biological activities - the antiproliferative and pro-apoptotic effects of JFE in estrogen dependent / aromatase positive (MCF7 aro), and estrogen independent (MDA-MB 231) breast cancer
cells, and in a normal, non-tumourigenic (MCF-10A) breast cell line.

It was found that JFE contained 3.5% anthocyanins (as cyanidin-3-glucoside equivalents) which occur as diglucosides of five anthocyanidins (glycosyl; delphinidin, cyanidin, pelargonidin, peonidin and malvidin. In the proliferation assay, JFE was most effective against MCF-7aro cell lines. These studies suggested that JFE may have potential beneficial effect against breast cancer. [13]

Computational modeling showed that cryptotanshinone could bind to the SH2 domain of STAT3. These results suggest that cryptotanshinone is a potent anticancer agent targeting the activation STAT3 protein. It is the report that cryptotanshinone has antitumor activity through the inhibition of STAT3. [14]

The chemo preventive activity of polyphenols extracted from seedless grape cultivars was effective, as that of seeded variety and these may have beneficial effects in disease states, especially cancer. [15]

Fresh apples suppress mammary carcinogenesis and proliferative activity; they induce apoptosis in mammary tumors of the Sprague-Dawley rats. Tumor multiplicity decreased with increasing apple extracts. Histopathological evaluations of tumors were performed, the proportions of Adenocarcinoma masses decreased with increasing apple extracts. The expression of proliferating cell nuclear antigen (PCNA), cyclin D1, Bcl-2 decreased. And Bax expression and apoptosis increased with increasing apple extracts. These results demonstrate the potential capacity of fresh apples to suppress DMBA-initiated mammary cancer in rats. [16]

Novel ultrasound-targeted micro bubble destruction mediated by shRNA plasmid transfection targeting survivin inhibits gene expression and induces apoptosis of hela cells. Survivin is an attractive target for tumor growth inhibition and represents a significant approach to anticancer therapy. The survivin could be regarded as an ideal anticancer target for cervical cancer. Recombinant expression plasmid of shRNA targeting survivin gene mediated by ultrasound targeted micro bubble destruction technique could effectively inhibit the expression of target gene and induce cell apoptosis. [17]

Glycohydrolase (PARG) is a catalytic enzyme that cleaves ADP-ribose polymers synthesized by members of the poly(ADP-ribose) polymerase (PARP) family of enzymes. Biological function of PARG-therapeutic potentials of PARG inhibition in path-physiological conditions such as inflammation, ischemia, stroke and cancer chemotherapy. [18]

The UDP Glucuronosyl Transferase, a family of metabolizing enzymes that are responsible for the deactivation and clearance of TAM (tamoxifen) and TAM metabolites, and how inter individual differences in these enzymes may play a role in patient response to TAM. [13] Endoxifen is the primary metabolite responsible for the overall effectiveness of tamoxifen in the treatment of ER positive breast cancer. [19]

Tumours must get their oxygen fix, otherwise invasive tumour growth and spread can occur. One way of quelling oxygen deprived tumours might be through manipulating the oxygen sensor PHD2. [20]

Massive muscle wasting affects most patients with cancer, and is often implicated in deaths. It’s thought that myostatin, a protein that inhibits muscle growth, and the other molecules in the same biochemical pathway regulate this process, called muscle cachexia. H.Q Han at Amgen researched in thousand oaks, California, and his team tested whether a molecule that interferes with a receptor for myostatin could prevent muscle cachexia in mice. Mice with cancer that were given the compound showed a complete reversal in muscle loss, as well as prolonged survival. [21]

Approved by US food and drug administration on 15 November, the highly complex molecule Halaven (eribulin mesylate) is the product of nearly 25 years of struggle in the lab. Eribulin is a synthetic compound that mimics part of the structure of halichondrin B, a molecule found in sea sponges, Halichondria okadai. Few years later scientists eyed in the halichondrin B structure and decided to take a crack at it. Researchers at the natural products branch of the US national cancer institute (NCI) in Frederick, Maryland, had discovered that halichondrin B fights cancer cells by inhibiting a protein compound of the cytoskeleton—the internal lattice work of rods and filaments that gives a cell its shape. That protein, called tubulin, is needed to support the rigid growth of the cancer cells and is the target of several other cancer chemotherapies, including taxol (paclitaxel). [22]

A genome wide association study (GWAS) has shown that single nucleotide variants within the LMO1 locus are associated with neuroblastoma, a childhood cancer of the sympathetic nervous system. LMO1 encodes a transcriptional regulator previously linked to cancers. Acquired structural variations in the same locus is common in patients with neuroblastoma, suggesting that loci identified through GWAS approaches might be prone to somatic alterations and so to identify potential therapy targets and biomarkers of cancer aggressiveness. [23]

Resistance of tumour cells to chemotherapy can severely affect the efficacy of this anticancer treatment. The non-tumour cells of the organ in which the tumour resides may aid the emergence of such resistance. Gilbert and Hermann treated the mice with doxorubicin—a DNA damaging chemotherapeutic agent that is often used to treat human cancers, including lymphomas and breast carcinoma. It was noted that, in often cases, tumor cells in most organs respond to this drug, but some cells survive and are eventually detectable, in this case its mainly in the thymus gland. They found that doxorubicin induces changes in the expression of several genes in the thymus. Among the genes affected, two seem to be the possible culprits in chemo resistance: the gene encoding the cytosine

IL-6 and that encoding a protein called Timp-1. One more detailed studies of IL-6, Gilbert and Hermann find that the source of this protein is thymic blood vessels. This observation adds to previous studies, which suggested that endothelial cells (which line blood vessels) contribute to tumour growth by secreting cytokines— or as they more aptly called, Angiocrine.

A stress response signalling pathway involving the enzyme p38 MAPK mediates acute IL-6 release by endothelial cells. It's found that IL-6 subsequently acts in a paracrine manner to promote the survival of a small number of doxorubicin–treated tumour cells that lurk in the thymus and eventually cause extensive metastases. IL 6 achieves this by inducing the expression of BCL-XL—a protein that inhibits programmed cell death. [24]

A new study in zebra fish shows that Birc 2, a member of the inhibitor of apoptosis (IAP) family, is required for the endothelial cell survival. This discovery highlights an important in vivo function of this molecule and suggests potential avenues for the development of new antiangiogenic therapies.

Death of blood vessels, especially if there are too many of them, has become a promising strategy to treat cancer patients and prevent blindness. Antiangiogenic agents that inhibit the formation of new blood vessels also act by causing vessel death. Using an elegant series of genetic studies in zebra fish, Santoo et al., discovered that Birc2 (also termed as clap1 or IAP1) an inhibitor of apoptosis, is crucial for the survival of endothelial cells, which line the inner portion of blood vessels.[25]

An in depth genetic analysis had identified several gene alterations associated with prostate cancer. Charles sawyers and his colleagues at the memorial Sloan- Kettering cancer center in New York analyzed protein expression and the number of copies of genes in 218 prostate cancer samples, including some that had metabolized to other parts of body. They also analyzed 12 prostate cancer cell lines and sequenced 157 genes of particular interest from a subset of the samples. The researchers identified three genes as potential tumour suppressors in some prostate cancers and found that differences in copy number of certain genes indicated clear sub groups of patients with high or low level of tumour progression. [26]

Malanoma–associated antigens such as MART-1 or tyrosinase, which are candidate targets for treatment. Interestingly, xenograft tumours had higher fractions of CD271+ cells. This could mean either that the xenografting process selects for a higher fraction of tumour initiating cells, or that cells do not express CD271+ gain tumour-initiating potential with a change in their environment—from primary tumour in the xenograft. Exploring these two possibilities, and whether markers such as CD271 for some of their meaning in a xenograft setting (or in a cell culture), deserving investigation. In particular to resolve some of the discrepancies, more human melanoma samples must be examined. [27]

Zebra fish cells with the propensity to give rise to tumours behave similarly to wounded tissue, and call for assistance from the immune system. The authors expressed a cancer associated mutant form of the ras protein in zebra fish (danio rerio). Because zebra fish larvae are translucent; the team was able to visualize fluorescently labeled immune cells as they responded to the transformed cells. Cells expressing mutant Ras, and their healthy neighbors, released hydrogen peroxide, attracting immune cells called neutrophils and the macrophages, which tethered themselves to the transformed cells. Blocking hydrogen peroxide synthesis and to the recruitment of immune cells—slowed the proliferation of transformed cells, suggesting that early immune responses may support tumour development. [28]

Protein kinase CK2, a protein serine/threonine kinase, plays a global role in activities related to cell growth, cell death and cell survival. CK2 has a large number of potential substrates localized in diverse locations in the cell including, e.g., NF-κB as an important downstream target of the kinase. In addition to its involvement in cell growth and proliferation it is also a potent suppressor of apoptosis, raising its key importance in cancer cell phenotype. CK2 has been found to be dysregulated in all cancers examined demonstrating increased protein expression levels and nuclear localization in cancer cells compared with their normal counterparts. CK2 plays a global role in control of cell growth and proliferation, and even more interestingly an equally major role in control of cell death.

Since the cancer cell phenotype has the consistently remarkable features of deregulated cell growth (elevation) and cell death (suppressed apoptosis), the observation that CK2 is elevated in cancer cells provides a key link of the kinase to neoplasia. While it was known for a long time that CK2 plays a role in cell growth and proliferation in normal and cancer cells, the more recent demonstration that CK2 was also a potent suppressor of apoptosis has squarely placed the functionality of the kinase in the cancer cell phenotype.

The association of CK2 with neoplasia has been known for a long time. Studies on diverse type of cancers have demonstrated that CK2 is uniformly elevated in all cancers examined. Interestingly, the elevation is noted at the level of protein rather than a significant change at the level of the enzyme message. It is well known that two of the most consistent features of cancer are deregulated proliferation and deregulated apoptotic activity. Thus, while CK2 was known to affect proliferation in both normal and cancer cells, the observation that CK2 potently suppressed apoptosis provided a vital link of the kinase to the cancer cell phenotype. It was recently suggested that a common denominator of diverse cancer cells may be an addiction to CK2. Under normal circumstances, cells resist even a modest up-regulation or down-regulation of cellular CK2. In the case of cell transformation, it appears that transformed cells acquire a new base level of CK2 and tend to maintain it in a stable manner analogous to that in normal cells, although in this case the cells have a dysregulated level
of CK2 compared with that in the original normal cells.

Various observations suggest that a relatively small change in the balance of CK2 expression can have a large impact on cellular homeostasis. It was observed that cancer cells, where the CK2 protein expression is already perturbed, seem to be even more sensitive than normal cells to inhibition of CK2 activity or expression. By the same token, although CK2 by itself is not an oncogene, modest up-regulation of CK2 can impart an oncogenic potential to the cells, as observed in experimental animal studies showing the remarkable contributory oncogenicity following increased expression of CK2. For example, overexpression of CK2α in p53 deficient mice or with c-myc or Tal-1 in transgenic mice resulted in a significant increase in the incidence of leukemia and lymphoma in mice. Likewise, incorporation of CK2α with MMTV produced a transgenic mouse model of breast cancer with several features resembling the human disease.

The importance of CK2 as a target for cancer therapy is derived from the following key considerations:

1. CK2 appears to be profoundly responsive to modulations of mitogenic signals from numerous initiating events in cells.
2. Down-regulation of CK2 expression affects inflammatory, angiogenic, and drug efflux pathways to the benefit of cancer cell elimination.
3. Dysregulated elevation of CK2 in cancer cells reflects the pathologic status of the tumor.
4. CK2 down-regulation impacts not only cell growth and proliferation but also apoptotic activity in cancer cells, making its targeting a two-edged sword.
5. CK2 is indispensable for cell survival, and as far as we know there appear to be no redundant pathways to compensate for its down-regulation.

The approaches being proposed are to use small molecule chemical inhibitors of CK2, a peptide inhibitor to block CK2 phosphorylation sites in CK2 substrates, and molecular down regulation of CK2 using antisense or siRNA. Targeting CK2 for cancer therapy raises the issue of its ubiquitous and essential regulation of CK2 using antisense or siRNA. Targeting CK2 for molecular down-regulation of CK2 substrates in the cell and a wide range of pathways that pertain to cell growth and proliferation, cell death, inflammation, migration, and angiogenesis. Aberrant activation of NF-κB has been documented in several cancers including mammary gland, prostate, and head and neck cancer. The activation of NF-κB in response to upstream signals is achieved by release of the inhibitory complex with IκBs, whose phosphorylation by various kinases including CK2 results in its degradation. Upon release, NF-κB (e.g., p65/p50) is translocated to the nucleus where it binds to regulatory sites of a variety of genes.

However, it appears that normal cells exhibit relative resistance to induction of apoptosis in response to agents such as antisense CK2α ODN or inhibitors of CK2 relative to cancer cells. The use of small molecule inhibitors or peptides to block CK2 phosphorylation sites in vivo is not based on protected or targeted delivery of these agents, relies on the pharmacologic window; however, their future success remains to be determined with regard to the potential of toxicity to normal cells and also the issue of tumor cell drug resistance, which may contribute to the problem of efficacy of these agents in vivo.

The focus has been on the utilization of molecular down-regulation of CK2 with attempts to do so specifically in cancer cells while sparing the normal cells in vivo. Starting with antisense CK2α ODN to down-regulate CK2 in cell culture and in prostate cancer (PCa) and head and neck squamous cell carcinoma (HNSCC) xenografts, it was originally demonstrated that potent tumor cell death is achieved in these experimental models. More recently, it has been devised novel antisense and siRNA constructs that down regulate both α and α’ subunits of CK2, thus ensuring more complete down-regulation of CK2 in vivo.

To achieve the goal of specific molecular down regulation of the targeted signal in tumors, a novel sub-50 (s-50) nm (i.e., less than 50 nm size) tenfibgen nano-capsule has been developed to deliver the CK2 targeting agent specifically to primary and distant tumors in vivo. Tenfibgen (TBG), the nanocapsule material, is a sub domain (fibrinogen binding fragment) of tenascin C.

The novel s-50 nm nano-encapsulation process to date displays many attributes of a potential clinically applicable in vivo delivery system. The resulting product is an ultra small neutrally charged particle, with a protective shell of the targeting ligand having a non-ordered surface stabilized by crystallization. For tumor targeting, a protein ligand, tenfibgen (TBG), enables tumor specific accumulation due to the increased expression of tenascin receptors specifically on the tumor cells, with negligible uptake observed by the reticuloendothelial system (RES) or other organs.

The s-50 nano-capsule is also suitable for magnetic resonance imaging (MRI) with demonstrated ability to overcome compartmental boundaries in vivo. The s-50 TBG nano-capsule containing antisense or siRNA directed against CK2 protects the nucleic acid in a tumor cell-specific protein ligand shell during circulation and releases the cargo within the cell following entry via the caveolar pathway, thereby bypassing the endosomal trap.

CK2 down-regulation: Since CK2 impacts over 300 potential substrates in the cell and a wide range of pathways that pertain to cell growth and apoptosis, it is likely that its down regulation would have a vast reach on activities that regulate cell function. Consistent with this, NF-κB is among the various pathways that have received considerable attention pertaining to a link with CK2 signaling.

NF-κB is known to have a broad role in regulation of many genes involved in diverse processes, among which are those relating to cell growth and proliferation, cell death, inflammation, migration, and angiogenesis. Aberrant activation of NF-κB has been documented in several cancers including mammary gland, prostate, and head and neck cancer. The activation of NF-κB in response to upstream signals is achieved by release of the inhibitory complex with IκBs, whose phosphorylation by various kinases including CK2 results in its degradation. Upon release, NF-κB (e.g., p65/p50) is translocated to the nucleus where it binds to regulatory sites of a variety of genes.
Further recent investigations along these lines undertaken in HNSCC have demonstrated differential responses of the NF-κB and TP53 pathways upon modulation of individual subunits of CK2. Studies on the activation of NF-κB in mammary gland and head and neck cancer demonstrated the involvement of CK2 in this process. Further, it is of note that CK2 is also involved in the phosphorylation of p65 directly thereby influencing its activity. Interestingly, activation of p65 and a related gene cluster is also linked with repression of tumor suppressor TP53 mRNA and protein expression in a subset of head and neck squamous cell carcinomas retaining wt TP53 genotype (HNSCC). Involvement of CK2 in modulating the activity of TP53 has also been noted, thus providing a possible link in these various pathways.

Knockdown of individual subunits of CK2 demonstrated a differential decrease of gene expression of not only NF-κB but also cell survival (BCL-XL) and cell cycle progression (CCND1) genes, whereas an increase of TP53 family genes known to promote growth arrest and apoptosis (p53 and Tap63) was observed. Knockdown of CK2α demonstrated a significant decrease in ITGA3 and ITGB4, while knockdown of CK2α′ resulted in decrease of ITGA6.

The angiogenic factor VEGF was significantly reduced by down-regulation of both α and α′ subunits of CK2. The involvement of CK2 in the process of angiogenesis has also been documented previously. Likewise, altered expression of certain integrin genes (ITG) involved in HNSCC adhesion and migration has been previously reported. Based on the observations that CK2 influences the expression of integrin genes in HNSCC, a further analysis of the effects of down regulation of CK2 subunits α and β on wound healing showed a marked inhibitory effect; these observations have provided novel information on the important role of CK2 in cell migration.

Different studies on the effects of various subunits of CK2 on induction of cell death also demonstrated that down-regulation of α but not α′ or β subunit was most prominent in inducing cell death in cultured HNSCC cells, analogous to previous observations in prostate cancer cells. Analysis of cell cycle under these various conditions suggested similar increases in cells arrested in G0/G1 in each case, but specific decreases in S phase by knockdown of CK2α and CK2α′ while that of CK2β resulting in a decrease in cells in G2/M phase. The therapeutic implications of these observations are highlighted by observations that modest down-regulation of CK2α in cells sensitizes them to agents such as TRAIL or etoposide, by shown that down-regulation of CK2 also sensitizes HNSCC to cisplatin. Further, studies were undertaken to examine the \( \text{in vivo} \) effects of down-regulation of CK2 by employing anti-CK2α/α′ ODN which target both the CK2α and CK2α′ subunits in the s-50 nm TBG nano-capsule formulation delivered systemically to a Xenograft model of HNSCC in mice.

The results demonstrated potent induction of apoptosis in tumor cells \( \text{in vivo} \) associated with down-regulation of CK2α and CK2α′ expression, a decrease in total NF-κB p65, and decreased p65 serine 536 and serine529 phosphorylation. Additionally, other genes related to growth and survival such as Cyclin D1, BCL-XL, and BCL2 demonstrated decreased expression while TP53 and p63 were increased. Other studies have investigated the interaction of CK2 with p53; it is noted also that p53 is not required for induction of apoptosis on down-regulation of CK2. The involvement of the downstream pathways relating to NF-κB and TP53 that respond to down-regulation of CK2 \( \text{in vivo} \) is illustrated in. Together with previous observations on the therapeutic effectiveness of knocking down CK2α, our recent studies further highlight the importance of targeting both CK2α and CK2α′ as a novel and potentially key strategy for targeted cancer therapy.

The availability of the s-50 nm TBG nano-capsule to deliver the therapeutic agent (such as antisense, siRNA, or chemical inhibitors for CK2) has important implications as it provides for the first time a means to target cancer cells while sparing normal cells \( \text{in vivo} \), and thus obviating issues relating to potential host toxicity as a result of CK2 down-regulation in general or from the nano-capsule, which includes a normal tissue protein. Given that down-regulation of CK2 causes death in diverse types of cancer cells, it was postulated that this therapeutic modality could find application in cancers other than prostate cancer and squamous cell carcinoma of head and neck that we have studied.

Thus the molecular down-regulation of CK2 achieved by its targeting \( \text{via} \) the s-50 TBG nano-capsule to a tumor cell specific manner has the potential of successful application to therapy of diverse types of cancers.[29]

Cancer is one of the commonest causes of patient death in the clinic and a complex disease occurring in multiple organs per system, multiple systems per organ, or both, in the body. With increasing evidence that the interaction and network between genes and proteins play an important role in investigation of cancer molecular mechanisms, it is necessary and important to introduce a new concept of Systems Clinical Medicine into cancer research, to integrate systems biology clinical science, omics- based technology bioinformatics and computational science to improve diagnosis, therapies and prognosis of diseases (30).

3.Cancer Bioinformatics: It is one of the multiple ways to concentrate bioinformatics methods in cancer, according to the specificity of disease metabolisms, signaling, communication, and proliferations. Clinical bioinformatics, an emerging science combining clinical informatics, bioinformatics, medical informatics, information technology, mathematics, and omics science together [31], can be considered to be one of critical elements addressing clinic challenges in early diagnosis, efficient therapies, and predictive prognosis of patients with cancer. Semantic models, containing genomic, transcriptomic and epigenomic data from melanoma samples with Gene Ontology data and regulatory networks constructed from transcription factor binding information, were applied for the interplay be-
tween a cell molecular state and its response to anti-cancer therapy. Multivariate assays, a process to characterize error introduced in the assay results from the intrinsic error in sample preparation and measurement of the contributing factors, were used to help and guide clinicians understanding the application to PAM50 centroid-based genomic predictors for breast cancer treatment plans and providing the uncertainty information in a usable way [32].

The miRTraIL is an integrative tool for analyzing comprehensive interactions of genes and miRNAs based on expression profiles to generate more robust and reliable results on deregulated pathogenic processes. It was suggested that miRTraIL may open avenues for investigating the regulatory interactions between genes and miRNAs for human diseases, including cancer, by integrating information on 20,000 genes, almost 1.000 miRNAs, and roughly 280,000 putative interactions [33]. Medical imaging should be one of important factors to be considered in the application of cancer bioinformatics, since the imaging in clinical pathology ultrasonic, computerized tomography nuclear magnetic resonance imaging, and positron emission tomography is one of the most necessary and important approaches in the “early and accurate” detection and diagnosis of cancer. Bioinformatics analyses of morphological features of masses and other abnormalities in medical images were initiated by selective extraction of target features by mathematical morphology and enhancement of the extracted features by two contrast modification techniques [34]. The algorithm described by Haustein and Schumacher in the Thematic Series on Cancer Bioinformatics in Journal of Clinical Bioinformatics [35] can simulate tumor growth and detect the formation of some metastases in advance of clinical detection in cells, on basis of clinical breast cancer data.

Cancer bioinformatics is expected to play a more important role in the identification and validation of biomarkers, specific to clinical phenotypes related to early diagnoses, measurements to monitor the progress of the disease and the response to therapy, and predictors for the improvement of patient's life quality. Of gene-, protein-, peptide-, chemical- or physic-based molecular networks may indicate the abnormality of early signals and the functioning, to finally carry out P4 medicine in cancer. However, cancer clinical bioinformatics is an important way to reach systems clinical medicine by combining clinical measurements and signs with human cancer tissue-generated bioinformatics, understanding clinical symptoms and signs, disease development and progress, and therapeutic strategy, and mapping relationships that integrate discrete elements that collectively direct global function within a particular -omic category with clinical examinations, pathology, biochemical analysis, imaging and therapies [31,36]. Ren and colleagues in the Thematic Series on Cancer Bioinformatics in BMC Bioinformatics have developed an algorithm named Optimization Tool for Clustering and Classification for multiple types of measurements, including proteomic and next generation sequencing data types [41].

The semantic heterogeneity of the data generated from microarrays, proteomics, epigenetics and next generation sequencing provided an ontology-based solution for querying distributed databases over service-oriented, model-driven infrastructures by integrating molecular, pathology, radiology and clinical data in an efficient manner [42]. A recent study performed a forward-genetic screen guided by genomic analysis of human hepatic cellular carcinoma, and found that a common genetic alteration in liver cancer (11q13.3 amplification) resulted in activation of FGF19 which caused the selective sensitivity to FGF19 inhibition through subsequent analysis with mouse models and RNAi [43]. Cancer bioinformatics and systems biology are expected to improve prevention, diagnosis and treatment through therapy design. For example, in the Thematic Series on Cancer Bioinformatics, published in Genome Medicine, Madhamshettiwar and colleagues evaluate nine different gene regulatory network inference methods and use the best-performing method to discover novel drug targets in ovarian cancer [44]. The classical techniques with ‘omic’ data sets and protein three-dimensional structure could form an indispensable backbone for computational cancer research [45].

All cancers arise as a result of changes that have occurred in the DNA sequence of the genomes of cancer cells. Over the past quarter of a century much has been learnt about these mutations and the abnormal genes that operate in human cancers. We are now however moving into an era in which it will be possible to obtain the complete DNA sequence of large numbers of cancer genomes. These studies will provide us with the detailed and comprehensive perspective on how individual cancers have developed.

Examining dividing cancer cells under microscope, they observed the presence of bizarre chromosomal aberrations. This led to the proposal that cancers are abnormal clones of cells...
characterized by and caused by abnormalities of hereditary material, following the discovery of DNA as the molecular substrate of inheritance and determination of its structure, this speculation was supported by the demonstration that agents that damage DNA and generate mutations also cause cancer. Subsequently, increasingly refined analysis of cancer cell chromosomes showed that specific and recurrent genomic abnormalities, such as translocation between chromosome 9 and 22 in chronic myeloid leukemia (known as the “Philadelphia” translocation) are associated with particular cancer types. Finally it was demonstrated that the introduction of the total genomic DNA from human cancers into phenotypically normal NIH3T3 cells could convert them into cancer cells.

All cancers are thought to share a common pathogenesis. Each is the outcome of a process of Darwin evolution occurring among cell populations within the microenvironments provided by the tissues of a multicellular organism. Analogous to Darwinian evolution occurring in the origin of species, cancer development is based on the two constituent processes, the continuous acquisition of heritable genetic variation in individual cells by more or less random mutation and natural selection acting on the resultant phenotypic diversity. Compared with the fertilized egg the cancer genome will also have acquired epigenetic changes which alter chromatin structure and gene expression which manifest at DNA sequence level by changes in the methylation status of some cytosine residues. Epigenetic changes can be subject to same Darwinian natural selection as genetic events, provided that there is epigenetic variation in the population of competing cells, that the epigenetic changes are stably heritable from mother to daughter cell and that they generate phenotypic effects for selection to act on.

DNA in normal cells is continuously damaged by mutations of both internal and external origins. Most of this damage is repaired. Mutation rates increase in the presence of substantial exogenous mutagenic exposures, for example tobacco smoke carcinogens, naturally occurring chemicals such as aflatoxins, which are produced by fungi, or various forms of radiation including ultra violet light. These exposures colorectal and endometrial cancers with defensive DNA mismatch repair due to abnormalities in genes such as MLH1 and MLH2, exhibit increased rates of acquisition of single nucleotide changes and small insertions and deletions at polynucleotide tracts. Other classes of such “mutator phenotypes” may exist, for leading to the abnormalities in chromosome number or increased rates of genomic rearrangement, although these are generally less well characterized are associated with the mutagen. The merit of an increased somatic mutation rate with respect to the development of cancer is that it increases the DNA sequence diversity on which selection can act.

The course of mutation acquisition need not be smooth and predecessors of the cancer cell may suddenly acquire a large number of mutations, this is sometimes termed “crisis” and can occur after attribution of the telomers that normally cap the ends of chromosomes, with the cell having to substantially reorganise its genome to survive. The known cancer genes run the gamut of tissue specificities and mutation prevalences, some for example TP53 and KRAS, are frequently mutated in diverse types of cancer whereas others are rare and/or restricted to one cancer type, for example colorectal and pancreatic cancer, abnormalities in several known cancer genes are common. Approximately 90% of the known somatically mutated cancer genes are dominantly acting, this is mutation of just one allele is sufficient to contribute to cancer development. The mutations in such cases usually results in activation of the encoded protein. The availability of the human genome sequence has also raised the possibility that DNA sequencing itself could become the primary tool for exploration of cancer genomes. This has prompted several pilot experiments. So far, most have sequenced large numbers of PCR products to detect the base substitutions and small insertions and deletions (collectively termed “point” mutations) present in the coding exons of protein coding genes. Typically, such studies have covered several hundred mega bases of cancer genome with designs ranging from hundreds of genes analyzed in a few hundred cancers to most of the 22,000 (approx) protein coding genes in 10 to 12 examples of a particular cancer class.

The effect of chemotherapy on the cancer genome has also been relieved by systemic sequencing experiments. For example, gliomas that recur after treatment with the DNA alkylating agent temozolomide have been shown to carry huge numbers of mutations with signature typical of such agents. Approximately 100,000 somatic mutations from cancer genomes have been reported in the quarter of a century since the first somatic mutations was found in HRAS. over the next few years several million more will be revealed by large scale. Complete sequencing of cancer genomes. These data will provide us with a fine grained picture of the evolutionary processes that underlie our commonest genetic disease, providing new insights into the origins and the new directions for the treatment of cancer.

The cancer inducing oncogenes may protect cells from anoikis by maintaining the cells glucose consumption. Cancer cells have an unbridled capacity for proliferation and invasion, thus cancer cells escape anoikis or viewed another way. Anoikis prevents cancer. Several oncogenes are known to hinder anoikis but the mechanisms by which they do this remain obscure. One oncogene, ERBB2 encodes the epidermal growth factor receptor, a cell surface protein that was activated in approximately 25% of breast cancers. ERBB2 expression might prevent anoikis in detached breast epidermal cells by effecting energy metabolism. They grew normal and ERBB2 over expression breast epithelial cells in a three dimensional culture systems that mimics normal mammary gland structure. Using this cultural system scafer etal show that ERBB2 expression rescues detached cells from energy depletion by maintaining their glucose uptake, specifically by activating the cancer inducing PI3K/AKT pathway.

Once in cells glucose may be metabolized through several pathways, including glycolysis, in which it's broken down to
pyruvate to generate ATP, the cells energy currency and the NADH, a mediator of ATP production. [47] Heidi Lyng and her colleagues at the Norwegian radium hospital in Oslo screened tumours from 102 patients with cervical cancer to look for changes in gene copy numbers and expression profiles. They found 57 candidate genes that were frequently gained or lost and which were linked to various well known tumour promoting process, such as carbohydrate metabolism and avoiding cell suicide. They also discovered some novel genes tied to resistance to chemotherapy. [48]

Cancer can become more deadly when tumour cells spread from one tissue type to another. A technique that uses two kinds of nanoparticle could help to trap and detect these rare cells in the blood stream, potentially enabling earlier cancer diagnosis. According to Vladimir Zharov University of Arkansas for Medical Sciences in Little Rock and his colleagues. [49] Patients undergoing irradiation for brain tumours often display signs of cognitive dysfunction, owing in part to loss of healthy neural stem and precursor cells. To investigate possible treatments, Charles Limoli and et al injected human embryonic stem cells into the brains of irradiated rats. After four months the researchers confirmed the cells survival in the rats brain and found that the animals performed much better in a place recognition task compared with irradiated rats that didn’t receive the transplant. [50]

The sox2 gene, famous for its role in helping to reprogram adult cells into stem cells, it’s also a cancer driver. A region around the sox 2 was frequently replicated in both diseases. Sox2 expressions is necessary for the growth of lung and esophageal squamous cell cancer lines. Over activating sox2 also turned normal cells cancerous with help from a couple of other genes. [51] A well known cock tail of genes can reset many adult cells to pluripotency, a state from which they can develop into almost any tissue. Now two groups have derived many adult cells to pluripotency, a state from which they can give rise to any kind of tissue and which were linked to various well known tumour promoting process, such as carbohydrate metabolism and avoiding cell suicide. They also discovered some novel genes tied to resistance to chemotherapy. [48]

A drug that targets a specific mutant protein in skin cancer improved survival in a clinical trial of 675 patients in advanced melanoma. The drug vemurafenib inhibits a mutated form of cell growth promoting protein BRAF. Mutations in this protein are found in about half of all melanomas. Paul Chapman of Memorial Sloan-Kettering cancer centre in network and his colleagues found that in their phase 3 trials of patients with metastatic melanoma and the BRAF mutation, almost half of those treated with vemurafenib responded to the drug, by contrast the response rate in patients receiving an older chemotherapy called decarbazine was only 5%. Six months after treatment, 84% of those who received vemurafenib were still alive, compared with 64% of those who received decarbazine. [55]

<table>
<thead>
<tr>
<th>Sl. no</th>
<th>Drug</th>
<th>Marker</th>
<th>Being tested in which cancers developed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>bevacizumab (avastin)</td>
<td>Genentech</td>
<td>Kidney, ovary, brain, prostate, liver, Pancreas, lymphoma, genital, gastroesophageal.</td>
</tr>
<tr>
<td>2.</td>
<td>sunitinib (sutent)</td>
<td>Pfizer</td>
<td>Breast, kidney, lung, liver</td>
</tr>
<tr>
<td>3.</td>
<td>sorafenib (nexavar)</td>
<td>Bayer</td>
<td>Lung, melanoma, pancreas.</td>
</tr>
<tr>
<td>5.</td>
<td>Axitinib</td>
<td>Pfizer</td>
<td>Kidney (pancreas suspended).</td>
</tr>
<tr>
<td>6.</td>
<td>xi184</td>
<td>Exelixis</td>
<td>Medullary thyroid cancer.</td>
</tr>
<tr>
<td>7.</td>
<td>BIBF1120</td>
<td>Boehringer ingelheim</td>
<td>Lung, gall bladder.</td>
</tr>
<tr>
<td>8.</td>
<td>cediranib (rectin)</td>
<td>Astra zeneca</td>
<td>Colorectal, brain, ovarian.</td>
</tr>
<tr>
<td>9.</td>
<td>aflibercept (VEGF trap)</td>
<td>Regeneron, sanofi Aventis</td>
<td>Lung, prostate, pancreas, colorectal.</td>
</tr>
<tr>
<td>11.</td>
<td>vandetanib (zactima)</td>
<td>Astra zaneca</td>
<td>Lung</td>
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The astounding renewal capacity the intestinal epithelial layer, in which most epithelial cells are replaced every week, places great demand on the cellular organization of the intestine and puts us at risk of developing cancer. Under normal conditions intestinal homeostasis is maintained by efficient interactions between stem cells residing in the intestinal crypt and the microenvironment. Recent developments have increased our understanding of the microenvironment derived signals that control intestinal stem cells, and had provided intriguing insight into the origin and organization of intestinal cancers. [54]
The above table states the list of angiogenesis inhibitors in the later stage of clinical development.

Massachusetts general hospital in Boston has for the past year and a half been offering people with cancer a novel diagnostic test. Instead of assessing tumors for a single mutation that will indicate whether a drug is likely to work out or not, the hospital tests patients for some 150 mutations in more than a dozen in cancer causing genes with the result being used to guide novel treatments, clinical trials and basic research.

Genetic testing for selected cancer patients in Britain’s government run health care provider, the national health service (NHS). This form of stratified medicine uses genetic information to group patients according to their likely response to a particular treatment. As the NHS treats millions of people each year, unprecedented numbers of suitable patients could be enrolled in the genetic profiling programme. The tests which would look for several dozen mutations in about a dozen genes linked to cancer, will be carried out on people with lung, breast, colorectal, prostate or ovarian cancers, or metastatic melanoma, who are being treated at six NHS hospitals. By genotyping patients for a broad array of cancer causing mutations, the new tests will make it easier to assign subjects to clinical trials. For example its broad genetic test detects a mutation in a gene called BRAF. [56]

Variation in a genomic region that contains the cancer associated gene ATM affects a patient’s response to the diabetes drug metformin. Two experts discuss the implication for understanding diabetes and the link to cancer. The variation occurs in a genomic region (locus) that also contains the gene ATM. ATM encodes a tumor suppressor protein involved in DNA repair and cell cycle control that is mutated in ataxia telangiectasia, a neurodegenerative disease associated with a predisposition to cancer. In a rat cancer cell line, that inhibition of ATM weakens metformin mediated activation of a metabolic enzyme, AMPK.

The genetic association between ATM and metformin sensitivity represents a triumph of modern pharmacogenetics, and it’s reasonable to hope that it will lead to fundamental insights into metformins mechanism of action and the regulation of carbohydrate metabolism. Metformin works mainly by reducing glucose production by the liver but there is still uncertainty about its mechanism of action at molecular level. The drug blocks a step in the aerobic production of cellular energy molecule ATP, activating a signalling pathway in which enzyme AMPK senses energetic stress within the cell. Nonetheless despite activating AMPK, metformin actually works independently of the enzyme. The discovery of role for ATM in modulating metformin responsiveness might provide a clue to the mechanism of the action of the drug. Another possibility is that ATM influences blood glucose levels through pathway parallel to but not the same as those modulated by metformin, and that its effects become apparent only with synergistic input from the drug. With the genetic clues now to hand, careful biochemical and cell biological studies should be performed to figure out the nature of the interaction between ATM and beneficial effects of metformin. [57]

A tumour suppressor protein that mediates DNA repair and has ties with a metabolic disorder this might sound farfetched. But in fact the reporter link between responsiveness to metformin and cancer gene is not without precedent. Previous work has shown the activation of AMPK by metformin requires the activity of kinase enzyme LKB1 was originally identified for causing an inherited cancer disorder, and it is one of the most commonly mutated genes in human lung cancer. The deletion of LKB1 in human mouse liver leads to loss of AMPK activity in that organ and to the development of metabolic dysfunction, including hyperglycemia and hepatic statuses symptoms resembles that of type 2 diabetes. [58]

A small clinical trial has shown promising results for a targeted therapy against one of the most aggressive and intractable forms of cancer: metastatic melanoma. The drug, named PLX4032, inhibits a mutated form of a protein called B-RAF. Mutated B-RAF found in up to 60% of all melanomas and drives cell proliferations. Keith Flaherty of Massachusetts General Hospital in Boston and his colleagues tested the drug in 16 patients with a particular B-RAF mutation and found that tumours shrunk by at least 30% in 11 of the patients. In a follow-up study of 32 participants, tumours shrunk in 24 and disappeared entirely in 2 patients. During the trial, five patients who did not have the mutation did not respond to the drug. [59]

Resistance to tumours to a common chemotherapy drug called cisplatin is linked to improved DNA repair in mouse models of lung cancer, researchers have found Cisplatin damages DNA and is used to treat various cancers. However, most tumours that respond to the drug eventually become resistant. [60]

Tyler Jacks at the Massachusetts institute of technology in Cambridge and his colleagues found that tumours that had been treated with cisplatin over 12 weeks cleared damaged DNA more quickly than previously untreated cancers. Long-term cisplatin use was also associated with higher expression of genes involved in DNA repair. Tumour angiogenesis is reduced in the Tc1 mouse model of Down’s syndrome [61]

The systematic characterization of somatic mutations in cancer genomes is essential for understanding the disease and for developing targeted therapeutics. Here we report the identification of 2,576 somatic mutations across approximately 1,800 mega bases of DNA representing 1,507 coding genes from 441 tumours comprising breast, lung, ovarian and prostate cancer types and subtypes. It was found that mutation rates and the sets of mutated genes varied substantially across tumour types and subtypes. Statistical analysis identified 77 significantly mutated genes including protein kinases, G-protein-coupled receptors such as GRM8, BAI3, AGTR1 (also called APLNR) and LPHN3, and other drug gable targets. Integrated analysis
of somatic mutations and copy number alterations identified another 35 significantly altered genes including GNAS, indicating an expanded role for alpha subunits in multiple cancer types. Furthermore, our experimental analyses demonstrate the functional roles of mutant GNAO1 (a Galphai subunit) and mutant MAP2K4 (a member of the JNK signalling pathway) in oncogenesis.

In many cancers, regulation of specific signaling molecules goes awry, affecting a host of other proteins and cellular processes. Proteomics is a useful systemic approach for identifying such extensive effects. [62] Acute myeloid leukemia in humans can be caused by different genetic changes that translate to markedly different responses to standard therapies. [63]

Human melanoma is resistant to treatment with retinoic acid, which is effective against several other cancers. But by activating the transcription factor SOX9, researchers at National Cancer Institute in Bethesda, Maryland, may have discovered a way to make retinoic acid effective after all. In a series of cell culture and tissue experiments, Vincent Hearing and his colleagues identified mechanisms by which promoting SOX9 activity slows cell division and sensitizes melanoma cells to the drug. [64] Oncologists use drugs that limit a tumor’s blood supply to prevent its growth. Although the initial effects of these drugs are beneficial to patients, new data suggest that their long term warrant further study. [65]

Cancer can be defined by six hallmarks, including uncontrollable growth, immortality and the ability to invade other tissues. Increasing evidence suggests that a seventh feature should make this list: “inflammation”. [66] Abnormal blood vessels inside tumours impede the delivery of oxygen to cancerous cells as well as affecting the cells’ sensitivity to chemotherapy. Meanwhile, oxygen starved tumors cells are more likely to metastasize. [67] Tumors must get their oxygen fix, otherwise invasion tumor growth and spread can occur. One way of quelling oxygen-deprived tumors might be through manipulating the oxygen sensor PHD2. [68]

Although smoking is the main cause of lung cancer, only 10% to 20% of smokers and former smokers actually develop the disease. The reasons for this and for the changes that lead to many cancers have eluded researchers for decades. The process of carcinogenesis takes years, if not decades. The search is on to discover and to validate the often-subtle, microscopic changes in the constituents in the blood, sputum, urine or tissue sample that herald cancer. Prior to oncogenic pathways, there is the possibility of identifying sluggish DNA repair mechanisms, changes in gene expression, or detecting the low level immune response to presence of a nascent tumour. A part of daily living, DNA frequently sustains damage. If not repaired, this can lead to mutations that replicate, resulting in abnormal and then cancerous growths. Certain mechanisms usually prevent this from occurring. The enzyme 8-oxoguanine DNA glycosylate (OGGI) repairs DNA by excising damaged bases. Biochemists zvi livneh et al discovered that levels of OGGI can also be used to predict an individuals risk of developing lung cancer. By measuring OGGI concentration in blood samples, livneh etal found that 40% of people with lung cancer and low levels of the enzyme compared to 4% of healthy individuals. Smokers with low OGGI activity were 5 to 10 times more likely to develop lung cancer than smokers with normal OGGI; when compared to non smokers with normal OGGI activity, the risk skyrocketed to 120 times more likely. The same blood test could be broadened to other cancers. For example, smokers with lower OGGI activity are 70 times more likely to develop head and neck cancer than non smokers with normal enzyme activity.

In the initial stages of cancer, the body is often able to recognize abnormal cell changes and raise a response, producing auto antibodies. However this response is limited, and in the later stages of cancer, the immune system becomes compromised and can no longer identify and attack cancer cells. By examining auto-antibody formation in presymptomatic individuals who later went on to develop lung cancer, samir Hanash, at the Fred hutchinson cancer centre in seattle, Washington, has identified three important antigens- annexin -1,14-3-3 theta and LAMR-1 regarded by the immune system as foreign. So far, specificity of these biomarkers is high but sensitivity lingers around 60%. The challenge for Hanash is to find additional candidate antigens that improve on the performance of this 3-antigen panel. [69]

Cyclin E drives cell proliferation and is found mostly in dividing cells, but is also present in the adult brain. In non dividing neurons in the mouse brain, the protein is involved in the memory formation. Neurons from mice in which the cyclin E gene was knocked out formed fewer synapses, or connections, and showed reduced synaptic transmission compared with normal mice. The knockout mice also exhibited memory impairments. The authors showed that cyclin E normally inhibits the enzyme cdk5, which regulates neuronal development. [70] Inhibition of BET recruitment to chromatin as an effective treatment for MLL fusion leukaemia [71].

The most frequently diagnosed cancers in industrialized countries are non melanoma skin cancers, including squamous – cell and basal cell carcinomas harbor a subset of cells known as cancer stem cells known as cancer stem cells, which initiate and propagate the tumor by a hitherto unknown mechanism. These cells secrete copious amounts of a growth factor that uses a two–pronged strategy to ensure that tumour growth continues indefinitely. They show that obstructing this dual activity causes stem cells to shrink and the tumour cells to regress. The growth factor that beck et al, find to be secreted in large quantities by skin cancer stem cells (CSCs) is VEGF. In a process known as angiogenesis, VEGF attracts endothelial cells that line blood vessels and stimulate their proliferation, creating a vascular network to supply the growing tumour with essential oxygen and nutrients. VEGF signals to endothelial cells by binding to a specific receptor, known as VEGFR2, on the cell membrane. Inhibiting VEGF signaling has already been shown to reduce squamous tumour initiation in vivo, as beck et al. Showed, selective inhibition of VEGF sig-
The protein HSP90 is a molecular chaperone—it assists in the correct folding of the other cellular proteins. Many of these hsp90 client proteins are over expressed and/or mutated in cancer and are involved in maintaining the cancerous state. HSP90 inhibition is therefore an attractive strategy for simultaneously blocking abnormal pathways that are crucial for many tumour types. However, understanding the mechanism that ensures the selective targeting of cancer cells by HSP90 inhibitors, and finding biomarkers to predict which cancers will be most sensitive to such treatment, has proved challenging. There are some 20 HSP90 inhibitors now in clinical trials. Their effects have been most impressive in breast cancers that over express a highly sensitive hsp90 client, the HER2 oncprotein, but that are resistant to the HER2 antibody drug trastuzumab. They are also promising in non small cell lung tumours that express the mutated oncogenic protein EML4-ALK, a similarly sensitive hsp90 client. However, in other cancer types HSP90 inhibition is less effective, despite the fact that the oncogenic constituents of such cancers are among hsp90 clientele. The best path to obtaining approval for widespread clinical use of these inhibitors may therefore be to apply them in a particular tumour subtypes that are driven by highly hsp90-dependent onco-proteins. HSP has a broad range of clients and is a potential advantage for therapy, but a challenge for predicting an individual patients response. Increased understanding of HSP90 client complexes in various tumour and healthy cells should help to pave the way for personalized clinical application of HSP 90 inhibitors, and could address a fundamental question—what makes a protein an hsp90 client?

Another family of genes that has been intensively studied for its role in ageing seems also to have an important function in maintaining genomic stability. This family of proteins is termed the sirtuins, a name based on the family’s founding member, the yeast protein silent information regulator 2 (SIR2). Yeast SIR2 has been implicated in the increase in lifespan that is seen after the caloric restriction and in both yeast and worms, over expression of sir2 is sufficient to extend lifespan. One common feature of the sirtuins is their enzymatic function as NAD dependent deacetylases for yeast SIR2; this biochemical activity is required for the proteins ability to regulate silencing, recombination and genomic stability. Seven mammalian sirtuins have been identified with the closest mammalian homologue to yeast sir2 being Sirt1. Establishing a role of Sirt1 in epigenetic silencing and genomic stability has been challenging. Over the last it has become clear that most humans cancers activate telomerase at some point during tumourigenesis, while this activity is largely absent in the most normal tissues. A significant number of human tumours can also maintain telomers by recombination based ALT mechanisms in the absence of telomerase. By activating a program of telomere maintenance, tumor cells can escape from replicative senescence; this ability was undoubtedly, essential for establishing the original HeLa cell line and for most, if not all, immortalized cells thereafter. Conversely, mice with short telomers are telomerase deficient and show age-dependent increase in chromosomal instability been known to occur in mammals for many years. Recent evidence indicates that the age dependent accumulation of somatic mutations might vary significantly between different tissue of the same organism and these genetic alterations might contribute to the stochastic variation in gene expression that is often seen in mammalian ageing.

Autophagy is regulated process for the removal of damaged proteins and organelles. Autophagy occurs under basal conditions and is stimulated by environmental factors such as starvation. There is evidence that proteins that are linked to tumorigenesis can regulate the rate of autophagy, with oncoproteins in general blocking and tumour suppressors stimulating the process. The removal of damaged cellular components, especially damaged mitochondria, might decreases the level of reactive oxygen species (ROS), which in turn might reduce genomic instability or forestall cellular senescence. Such mechanisms might allow moderate increases in autophagy to reduce the incidence of cancer and prolong lifespan.

In relatively simple organisms such as C.elegans, mutations that prolong lifespan are often intimately connected with the ability of the organism to withstand stress, particularly oxidative and metabolic stress. This strategic metabolic overlap has been made more concrete by observations of specific genes that link together the trait of lifespan, cancer and energetic. One such gene is Trp53, which encodes p53. There is growing link between p53 and cellular mechanism. This link has been strengthened by the recent reports that p53 regulates the transcription of two proteins, TP53 induced glycolysis and apoptosis regulator (TIGAR) and the SCO cytochrome oxidase deficient homologue 2(SCO2), which has key roles in the utilization of glucose and mitochondrial respiration, respectively.

Another pathway that allows cells and organism to changes in nutrient availability is the TOR signalling network. This pathway has been the subject of many reviews. A number of upstream regulators of TOR including PTEN, tuberous sclerosis 2 (TSC2), V –akt murine thymoma viral oncogene homologue 1 (AKT 1) and serine/threonine kinase11 (STK11, also known as LKB1) are frequently altered in human tumours. Similarly, the use of the TOR inhibitor rapamycin is currently being actively pursued as a treatment for human malignancies. The TOR pathway has also received renewed interest for its role in ageing. In many organisms, decreased TOR signalling is associated with the extension of life span. Similarly under some conditions, TOR signaling seems to be required for longevity benefits of caloric restriction in yeast. Similarly in mammalian cells, mammalian TOR (m TOR) seems to be an important regulator for overall mitochondrial metabolism. SDH mutations could be found in certain pheochromocytomas, a related tumour in the adrenal gland. In additional analysis of other unrelated families with paragangliomas showed that in these individual, tumours were associated with mutations in other SDH subunits.SDH is involved in two aspects of metabolism: it function as an enzyme in Krebs cycle (converting succinate to fumarate) as well as serving as complex 11 of the electron transport chain. Interestingly, inherited mutations in fumarate hydratase, another krebs cycle enzyme, have also been linked to a separate and equally rare inherited cancer syndrome. In both of these cases, tumours seem to arise secondary to increase in metabolic intermediates (succinate and fumarate, respectively). These intermediates seem to function, in part, by directly inhibiting the prolyl hydroxylase enzyme family, which controls the degradation of hypoxia inducible factor 1α (HIF1α).

As discussed, in some instances, such as cellular senescence or telomere shortening, strategies that protect us from cancer might hasten our rate of ageing in other situations such as autophagy or protection from genomic instability, cancer and ageing seem to share common, rather than antagonistic, aetiologies. Finally, a deeper understanding of molecular control of energy sensing and utilisation, including what regulates mitochondrial activity and how the nucleus, mitochondria, and cytoplasm communicate, provide new and fundamental insights into how we age and how a cancer cell emerges. These same barriers now appear to be intimately connected to how and why we age. Perhaps Henrietta's final gift to us is the growing realisation that somewhere within the curse of the cancer cells immortality there might also lie the secret of how we might understand and extend our life span.[74]

In the early 1990's immunologist Edgar Engleman discovered the way to treat cancer using a vaccine that harnessed the body's immune cells. He co founded a company –later named Dendreon –in 1992 to develop the vaccine, predicting that it would reach patient within a few years. Now, after some 20 years of successes and setbacks, Dendreon's prostate cancer vaccine provenge (sipleucel-T) may finally be nearing the market; the US food and a drug administration (FDA) is expected to reach a decision on its approval by 1may. If the vaccine is approved, it will mark a turning point for the field of therapeutic cancer vaccines, an approach that seemed promising but developed a disappointing reputation after several high profile failures in clinical trials. It would also offer a potential new treatment for patients with advanced prostate cancer, which killed more than 28,000usmen in 2008.

Provenge is much more complex than familiar vaccines against viruses, such as measles or human papilloma virus, the cause of most cervical cancers. The vaccine is tailor made for each patient by harvesting his dendritic cells- a type of immune cell –and exposing them to a cancer associated protein called prostatic acid phosphatase. Once infused back into the patient, the exposed cells should trigger an immune assault on tumour cells. Many first – generation cancer vaccines such as PANVAC, a pancreatic cancer vaccine, were deemed safe but failed to demonstrate that they significantly slowed the progression of cancer. Because cancer associated antigens –such as those used in provenge –are also found at low levels in healthy tissue, and their ability to trigger a powerful immune response may be blunted.

A second generation of vaccines, designed to provoke a stronger immune response , is under development, with some scientists now focusing on antigens that are found only on tumour cells. One of the first vaccines to use this approach...
targets a mutant protein called EGFRv111 that is found in glioblastoma, an aggressive brain cancer. The vaccine is being jointly developed by drugs giant pfizer, based in NEWYORK, and celldex, a biotechnology firm headquartered in Nedham, Massachusetts. Compounds that modulate the immune response could have unwanted side effects, however a patient in clinical trial of stimuvax involving high doses of cyclophosphamide developed an acute inflammation of brain, which caused the FDA to put all stimuvax trials on hold. (Heidi Leford)

Genomic instability is one of the most pervasive characteristics of tumour cells and is probably the combined effect of DNA damage tumour-specific DNA repair defects, and a failure to stop or stall the cell cycle before the damaged DNA is passed on to the daughter cells. Although these processes drive genomic instability and ultimately the diseases process, they also provide therapeutic opportunities. One of the most pervasive characteristics of human tumours is genomic instability. Although the specific DDR (DNA damage response) defects are not known in most cancers, there are several examples in which there is an incontrovertible link between a particular DDR dysfunction and the neoplastic phenotype. For example 15% of sporadic colorectal tumours show an abnormal shortening or lengthening of dinucleotide repeat sequences this DNA mutation pattern, known as microsatellite instability, is probably caused by an inability to repair DNA replication errors when mismatch repair is defective. Microsatellite instability’s observed not only in sporadic colorectal tumours but also in familiar forms of diseases known as hereditary non-polyposis colorectal cancer (HNPCC). HNPCC is associated with loss of function mutations in mismatch repair genes, such as MSH2 and MLH1. Evidence is also building that the DDR is not only invoked but also dysfunctional at an early stage in the development of neoplasia. Markers of DSBs, such as nuclear H2AX foci (a histone phosphorylation event that occurs on chromatin surrounding a DSB), are markedly elevated in some precancerous lesions.

One hypothesis proposes that the original cause of these effects is oncogene activation. This activation of oncogene such as MYC and RAS stimulates the firing of multiple replication forks as part of a proliferative program. These forks rapidly stall, collapse and form DSBS because they exhaust the available Dntp pool or because multiple forks collide on the same chromosome, regardless of the mechanism stalled and collapsed forks normally invoke the DDR and cell cycle checkpoints that enable DNA lesions to be repaired before mitosis takes place. For precancerous lesions to progress to mature tumours, its thought that critical DSB signal transduction and cell cycle checkpoint proteins, such as ATM, ataxia telangiectasia and Rad3 related (ATR) and the master ‘gatekeeper ‘protein p53 become inactivated with these DDR components rendered dysfunctional, collapsed forks are not effectively repaired, and cells proceed through the cell cycle with DNA lesions intact, increasing the chance of mutagenesis.

PARP1 and parp2 are members of the PARP protein super family. The best understood role of PARP1 is in SSB repair a form of BER. PARP1 initiates this process by detecting and binding SSBS through a zinc finger in PARP protein. Catalytic activity of PARP1 results in the PARylation of PARP1 itself and the PARylation of series of additional proteins, such as XRCC1 and the histones H1 and H2B, when PARP activity is inhibited, SSB repair is compromised. The development of PARP inhibitors began with the observation nicotinamide, a product PARP catalytic activity, is itself a week PARP inhibitor, as are nicotinamide analogue, such as 3-aminobenzamide. The screening of chemical libraries and the subsequent chemical refinement of compounds have led to second generation PARP inhibitors (for example benzimidazole-4-carboximide NU1025), and to a third generation of clinically usable inhibitors, such as tricyclin lactam indole, AG014699, and phthalazinones, such as AZD2281(olaparib). For cancer therapy PARP inhibitors are potent chemosensitizers.

The preclinical work has paved the way for subsequent clinical studies of PARP inhibitors. Phase 1 studies has established the safety of olaparib, a potent PARP inhibitor, as a single agent and shown that significant and durable antitumor responses can be established in patients with BRAC mutant breast, ovarian or prostate tumours. Furthermore, olaparib does not seem to cause many of the side effects associated with the chemotherapies.

Many human cancers contain cells that share some of the self renewal and differentiation properties of stem cells. These cancer stem cells are thought to act as tumour-initiating cells that, after treatment, may potentially repopulate the therapy–resistant tumour.

| Table 2: Examples of DDR inhibitors in clinical use or in development. |
|---|---|---|---|
| **Class** | **Name** | **Stage of development** | **Cancer type** |
| Topoisomerase I inhibitor | Irinotecan | Licensed for use | Mainly colorectal cancers. |
| Topoisomerase II inhibitor. | Etoposide Phosphate | Licensed for use | For e.g. Testicular cancer, lung cancer, lymphoma etc |
| DNA protein kinase inhibitor. | CC-115 | Phase 1 study under way. | Advanced solid tumours, non hodgkin’s lymphoma and multiple melanomas. |
malignant tumour cells with a single strand of DNA is thought to limit the impact of DNA replication errors to the stem cell population. A number of studies have suggested that resistance to therapy is mediated by altered DDR activity in cancer stem cells, these may include controversial and unproven concepts such as immortal strand, model in which parental, but not newly synthesized DNA, is retained in stem cells after mitosis; retaining only the parental strand of DNA is thought to limit the impact of DNA replication errors to the stem cell population.

In mouse models, cancer stem cells deficient in p53 showed accelerated DNA repair activity, as well as high levels of AKT and WNT signalling, both of which promoted cancer stem cell survival after exposure to ionising radiations. In glioblastoma multiforme, a cancer stem cell has been characterized the expression of prominin(CD133; now known as PROM1). CD133, cells are enriched after irradiation of human glioblastoma multiforme, a cancer stem cell has been characterized the expression of prominin(CD133; now known as PROM1). CD133, cells are enriched after irradiation of human glioblastoma multiforme, a cancer stem cell has been characterized the expression of prominin(CD133; now known as PROM1). CD133, cells are enriched after irradiation of human glioblastoma multiforme, a cancer stem cell has been characterized the expression of prominin(CD133; now known as PROM1). CD133, cells are enriched after irradiation of human glioblastoma

<table>
<thead>
<tr>
<th>PARP inhibitor</th>
<th>Olaparib</th>
<th>Veliparib</th>
<th>Rucaparib</th>
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<tbody>
<tr>
<td></td>
<td>2 phase 11 studies completed, 9 additional phase 11 studies under way</td>
<td>16 phase 11 studies under way</td>
<td>2 phase 11 studies recruiting</td>
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<tr>
<td></td>
<td>Ovarian, breast, gastric colorectal and a range of other solid tumours.</td>
<td>Ovarian, breast colorectal and a range of other solid tumours.</td>
<td>Breast and other solid tumours.</td>
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With this role in mind, understanding the response to DNA damaging therapy in cancer stem cells, these may include controversy and unproven concepts such as immortal strand, model in which parental, but not newly synthesized DNA, is retained in stem cells after mitosis; retaining only the parental strand of DNA is thought to limit the impact of DNA replication errors to the stem cell population.

5. Treatment strategies:

Different heads of broccoli varied 20 fold in their contents of glucoraphanin. The specific variety, growing conditions, time of year, distance of transport and other factors all affect the concentration of phytonutrients. Working with John Hopkins plant physiologist Jed Fahey, Talalay found that broccoli seeds were 100 times richer in glucoraphanin than adult plants and certain varieties of seeds contained predictable amounts of molecule. Eating a known amount of Phytonutrients doesn't guarantee that a predictable amount of cancer fighting molecule will enter the blood stream. Differences can be traced to variations in the genes involved in the digestive processes. For example, the glutathione S-transferase M1 gene (GSTM1) influences the speed at which the body metabolizes sulforaphane and expels it in urine. The faster it happens; the less beneficial is the broccoli. GSTM1 gene is the best studied of the genes that influence phytonutrient metabolism, but it is just one of a rapidly growing list. For example, people who carry two copies of a particular variant of the UGT1A1 gene make about 30%-40% less than normal of a type of phase II enzyme.

One study has shown that people with this genotype derive more cancer protecting benefit from eating cabbage and carrot family vegetables—possibly because Phytonutrients in these foods boost UGT1A1 activity closer to normal. So depending on their intestinal bacteria, two people who eat the same amount of soy each day might receive not only different quantities of isoflavones but also different end products.

Between 30% and 50% of the people harbor bacteria that produce equol, which some scientists believe is one of the more beneficial forms of isoflavones; around 80% to 90% of people have bacteria that produce O-desmethylanogolensin, a less active molecule.

Many Phytonutrients are found in small quantities in bulky foodstuffs, or only in particular types of seasonal fruit and vegetables. This means it is impractical to eat enough to noticeably reduce cancer risk. For example, many berries are rich in Phytonutrients called anthocyanins, which are antioxidants and may have other cancer fighting effects as well. Martin led a team that genetically engineered a tomato (which has a few natural anthocyanins) to contain roughly the same concentration of anthocyanins as blueberries. In 2008, they showed that this deep purple tomato, known as Del/Ros1 N lived longer than mice fed either ordinary red tomatoes or standard labora-

Resveratrol suppresses human colon cancer cell proliferation and induces apoptosis via targeting the pentose phosphate and the talin-FAK signaling pathways - A proteomic approach.[76] Resveratrol (RSV) suppresses colon cancer cell proliferation and elevates apoptosis in vitro and/or in vivo; however molecular mechanisms are not fully elucidated. Particularly, little information is available on RSV’s effects on metabolic pathways and the cell-extra cellular matrix (ECM) communication that are critical for cancer cell growth. Pentose phosphate pathway (PPP), a vital metabolic pathway for cell cycle progression, was elevated and suppressed by IGF-1 and RSV, respectively in the HT-29 cell line. Enzymatic assays confirmed RSV suppression of glucose-6 phosphate dehydrogenase (rate limiting) and transketolase, key enzymes of the PPP. RSV (150 uM) suppressed, whereas IGF-1 (10 nM) elevated focal adhesion complex (FAC) proteins, talin and pFAK, critical for the cell-ECM communication. Western blotting analyses confirmed the suppression or elevation of these proteins in HT-29 cancer cells treated with RSV or IGF-1, respectively.

Proteomic analysis enabled us to establish PPP and the talin-pFAK as targets of RSV which suppress cancer cell proliferation and induce apoptosis in the colon cancer cell line HT-29. RSV (150 uM) suppressed these pathways in the presence and absence of IGF-1, suggesting its role as a chemopreventive agent even in obese condition. [77]

There is ample evidence that shows an inverse relationship between consumption of fruit/vegetable-rich diets and the risk of cancer at various anatomical sites. In this review, we will summarize recent advances on cancer prevention by resveratrol, a natural stilbene present in red wine, grapes, peanuts, and several other foods/drinks consumed in a typical American diet. Interest in resveratrol as a chemopreventive agent stems largely from the report by Pezzuto and coworkers [79] regarding its activities to inhibit initiation and promotion of hydrocarbon-induced skin cancer and progression of breast cancer in mice. Since then, a voluminous body of literature has been published on resveratrol, and several excellent reviews have been written on its numerous biological activities [80-85]. Some of the notable bioactivities of resveratrol include: anti-oxidant and anti-inflammatory activity; inducer of phase II enzymes; ability to interact with membranes and the mitochondria; inhibition of lipoxygenase; and thus, the synthesis of proinflammatory lipid peroxides and by-products. Resveratrol also suppresses malignant cell growth, induces cell cycle arrest, restores apoptosis, and down regulates the expression of cancer cell type specific genes. In addition, resveratrol also prevents the activation of procarcinogens and inhibits a myriad of molecular and cellular events in cancer cell types, which provide gain of function for the cells to survive and thrive in their primary site and at distant, metastatic sites. The source, chemical structure, and biological/biochemical effects of resveratrol are summarized.

As a polyphenolic stilbene, resveratrol is abundantly present in red wine, grape skin, peanuts, and several other foods/drinks consumed in a typical American diet. Interest in resveratrol as a chemopreventive agent stems largely from the report by Pezzuto and coworkers [79] regarding its activities to inhibit initiation and promotion of hydrocarbon-induced skin cancer and progression of breast cancer in mice. Since then, a voluminous body of literature has been published on resveratrol, and several excellent reviews have been written on its numerous biological activities [80-85]. Some of the notable bioactivities of resveratrol include: anti-oxidant and anti-inflammatory activity; inducer of phase II enzymes; ability to interact with membranes and the mitochondria; inhibition of lipoxygenase; and thus, the synthesis of proinflammatory lipid peroxides and by-products. Resveratrol also suppresses malignant cell growth, induces cell cycle arrest, restores apoptosis, and down regulates the expression of cancer cell type specific genes. In addition, resveratrol also prevents the activation of procarcinogens and inhibits a myriad of molecular and cellular events in cancer cell types, which provide gain of function for the cells to survive and thrive in their primary site and at distant, metastatic sites. The source, chemical structure, and biological/biochemical effects of resveratrol are summarized.

What is resveratrol?

- **Source:** red grape, peanut, red wine

- **Chemical structure:**

- **Biological/biochemical activity:**

The aromatic stilbene core structure and hydrophilic side groups of resveratrol support the hypothesis that its chemopreventive potential may in part lie in ability to interact with and modulate cellular target proteins, designated RTPs in resveratrol-responsive cells. It is hoped that the perspectives we have presented will offer vital answers to the quest to reduce the pain and suffering engendered by neoplastic diseases and to promote optimal health. The hope offered by diet-derived ingredients and phytochemicals is worthy of further attention and research.

6. Conclusion:

Biotechnology has remarkably produced new therapies and vaccines including products to treat cancer and several autoimmune diseases. Humanized monoclonal antibodies also represent for anticancer therapeutics. Genes like Heat Shock Proteins HSP27, HSP70 & CK2 gene act as molecular chaperons for cell proliferation & cell death, thus act as key target for cancer therapy.

Cancer bioinformatics, an emerging strategy for clinical research. S-50nm TBG nano-capscule to deliver the therapeutic agents (SiRNS, antisense or chemical inhibitors for CK2) has important implications to target cancer cells sparing normal cell in vivo, thus obviating the issue of host toxicity.

Network biomarkers with protein-protein interactions were investigated with integration of knowledge on protein annotations, signalling pathway. ERBB2 expression might prevent Anoikis in detached breast epidermal cells by effecting energy metabolism. Drug vemurafenib inhibits a mutated form of cell growth promoting protein BRAF. Even cisplatin is linked to improved DNA repair.

Broccoli seeds are the rich source of glucorophanin (phytonutrient), that influence the GSTM1 gene thereby acting as an anticancer agent and also the anthocyanin rich tomato could make potential anticancer foods including the engineered tomato 1000times higher than in red wine.

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