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Drug repurposing in Oncology: Opportunities and challenges

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ABSTRACT

The strategy of using existing drugs originally developed for one disease to treat other indications has found success across medical fields. Such drug repurposing promises faster access of drugs to patients while reducing costs in the long and difficult process of drug development. However, the number of existing drugs and diseases, together with the heterogeneity of patients and diseases, notably including cancers, can make repurposing time consuming and inefficient. In a current research, it is also found that cancer cells have a property of intra-tumor heterogeneity i.e., formation of sub-group of cancer cells that shows more complexity in revelation of their genetic makeup and this property gives birth to a sub-class of cancer cells that are known as cancer stem cells (CSCS).

Keywords: Repurposed drug, Drug development,Cancer stem cells, Heterogeneity

INTRODUCTION

Cancer remains to be a major global healthcare burden as 18.1 million new cases and 96 million death occurred 2018 on the basis of report from the international agency for research on cancer(IARC)[1].

Most common types of cancers occurring in humans are lung, female, breast and colorectal. There are high chances of death in these cancer patients on factors based on early detectionchemo-resistance or tumourheterogenicity as well as chances of metastases.

Metastatic cancer or surgically non-respectable tumour show five years mortality above 909 in chronic cancer like pancreatic cancer and cytogenetically defined high risk acute myeloidleukaemia (AML) till present date aggressive cancer types has not been mainly due to therapeutic failure on another side a drug productivity cries appear in the pharmaceutical research and development area (R&D)[2]and they prepare to the clinic. In fact, although investment in the last decade.[3] The lack in production of drug and being approved is become more challenging fortherapeutic innovates the discovery and development process of therapeutic innovation (new drug) becomes long and expensive with low overall probability of skill.

The 70% of project failed in phase-1 and phase-3 phase-2 failure is due poor pharmacokinetic properties of drug under examination [4,5]

This may be due poor relationship between dose exposure its associate with the target of interest among the major causes we recall doses for treatment that is too low or too high.[6]

The possible positive effect is too short to detect the treatment duration and there will be no predictive target pathway related biomarker. The drug development pipeline failure and time tobring new drug to the market raised and important issues On R&D cost productivity potentially reducing their R&D investment at least in certain area of research the increased cost of novel approved cancer therapeutic are raising the important issues on treatment cost.[7,8]

In recent there is essential need for an automotive approach to shortly advance in cost effective manner the availability of novel and effective anticancer therapeutics. An intriguing approach in anticancer pharmaceutics is to review old FDA approved drugs for novel therapeutic indication also known as drug repurposing

The drug repurposing primary advantage is of course involved with time and cost issues. Drug re-purposing reduces the cost and risk which are involved with drug it also reduces the time intervalbetween drug discovery and functionality to the patient due to compensability of high amountpharmacokinetics and pharmacodynamics and clinical data [9, 10]

In the content of oncology its useful mention two additional loss late advantage of drug repurposing in fact when we perform experimental oncology these offers a uninterrupted validation of new targets and drugs at the sometime reducing the effectiveness of drug discoverydue to drug repurposing the approved drug with the potential of combinational treatment to improve the efficacy which has already existing in anti-cancer is beneficial [11,12]

Last but not least drug repurposing offer the opportunity to identify therapeutic drugs for the treatment of rare cancer which are neglected by pharmaceutical companies due to marketing The drug repurposing also helpful to those drug which are present with in the market to improve the revenue and identify new indication to extend the patient life of drug. [13]

It also helps to protect the compares from intellectual property against competitors. By the think drug repurposing will set more and more successful stage in future cancer therapeutics scenario which will be effective and useful.

Pathophysiology of cancer

Cancer is fundamentally a disease of tissue growth regulation. Inorder for a normal cell to transform into a cancer cell, the genes that regulate cell growth anddifferentiation must be altered.

The affected genes are divided into two broad categories Oncogenes are genes that promote cell growth and reproduction. Tumor suppressor genes are genes that inhibit cell division and survival. Malignant transformation can occur through the formation of novel oncogenes, the inappropriate over-expression of normal oncogenes, or by the under-expression or disabling of tumor suppressor genes. Typically changes in multiple genes are required to transform a normal cell into a cancer cells.Genetic changes can occur at different levels and by different mechanisms. The gain or loss of an entire chromosome can occur through errors in mitosis. More common are mutations, which are changes in the nucleotide sequence of genomic DNA.

Large-scale mutations involve the deletion or gain of a portion of a chromosome. Genomic amplification occurs when a cell gains copies (often 20 or more) of a small chromosomal locus,usually containing one or more oncogenes and adjacent genetic material. Small-scale mutations include point mutations, deletions, and insertions, which may occur in the promoter region of a gene and affect its expression, or may occur in the gene's coding sequence and alter the functionor stability of its protein product. Disruption of a single gene may also result from integration of genomic material from a DNA virus or retrovirus, leading to the expression of viral oncogenes in the affected cell and its descendants.Replication of the data contained within the DNA of living cells will probabilistically result in some errors (mutations). Complex error correction and prevention is built into the process and safeguards the cell against cancer. If a significant error occurs, the damaged cell can self-destruct through programmed cell death, termed apoptosis. If the error control processes fail, then the mutations will survive and be passed along to daughter cells [14]

Some environments make errors more likely to arise and propagate. Such environments can include the presence of disruptive substances called carcinogens, repeated physical injury, heat, ionizing radiation or hypoxia. The transformation of a normal cell into cancer is akin to a chain reaction caused by initial errors, which compound into more severe errors, cache progressively allowing the cell to escape more controls that limit normal tissue growth.

This rebellion-like scenario is an undesirable survival of the fittest, where the driving forces of evolution work against the body's design and enforcement of order. Once cancer has begun to develop, this ongoing process, termed clonal evolution, drives progression towards more invasive stages. Clonal evolution leads to intra-tumor heterogeneity (cancer cells with heterogeneous mutations) that complicates designing effective treatment strategies.

Characteristic abilities developed by cancers are divided into categories, specifically evasion of apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals. sustained angiogenesis, limitless replicative potential, metastasis, reprogramming of energy metabolism and evasion of immune destruction.

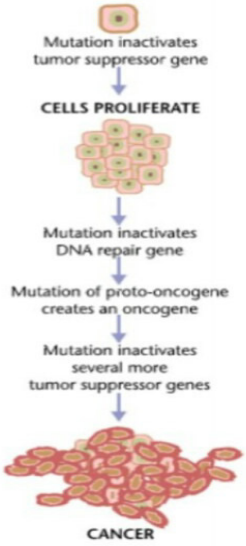

Figure: -1 Pathophysiology of cancer

Significance of cancer therapy

Since last decade cancer is successful in developing its identity as an organ whose complex approaches were difficult to detect as they have their genetic makeup completely different from that of healthy cells. The biology of cancer cells can only be identified when they are inspected on the individual basis. This also helps to know about the microenvironment that is building around the tumor cells. The mechanism of cancer cells can only be understood by isolating a specific group of homogenous cells and considering property of individual cells in that group.

There is a group of cells that contributes to the biology of tumor microenvironment and the signaling system that helps to control the function of individual cells as well as that of the group of cancerous cells. In a deep observation, it is found that there is a compartment formation by neoplastic epithelial cells which is clearly differentiated from mesenchymal cells that are responsible for generation of stroma associated with cancer [15]

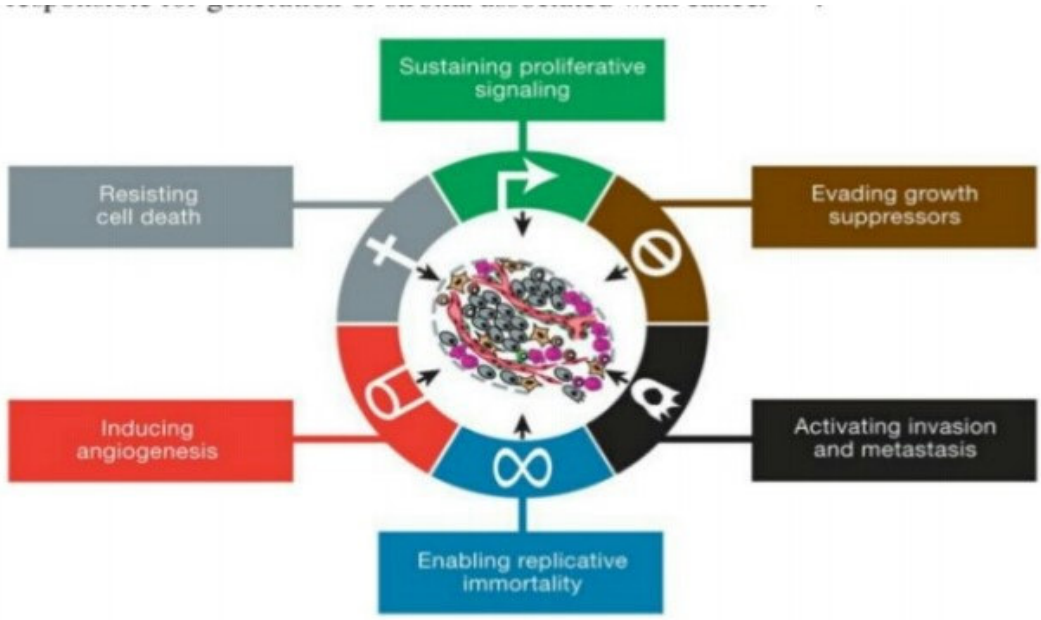

Figure-2 the hallmarks of cancer

Cancer cells and cancer stem cells: The foundation or strength of this disease is the type of cells it produces that remains unidentified due to constant change in their genetic makeup and surviving for contributing in severity of disease. From traditional times the hologenetic cell population is one of the reasons for progression of cancer. This process starts when an increase is seen in unstable spawn clonal population that is combined with hyper proliferation of cells.

This shows clonal heterogeneity in cancer cells. In some tumors it is found that histopathology of human cancer is very vast and diverse, differentiated by degree of growth, vascularity, proliferation property invasiveness and production of severe inflammation at the sote of attack. In a current research, it is also found that cancer cells have a property of intra-tumor heterogenicity i.e., formation of sub-group of cancer cells that shows more complexity in revelation of their genetic makeup and this property gives birth to a sub-class of cancer cells that are known as cancer stem cells (CSCS).

Hence, the research is still going it is not yet confirmed that these cancer sub-cells are sub part of all cancer cells, but it is assured that it is found as a part of most of the tumor cells. In a study it is found that these cancer stem cells can be easily identifies by their property of giving rise to new stem cells when they are inoculated in the host mice model in the laboratories.

The function of newly generated stem cells can be identified by the expression of cancer stem cells marker that is also part of stem cells that are found at the site of prior tumor formation. These cancer stems are initially found only during pathogenesis of hematopoietic malignant tumors but few years from then, it is also detectable in solid tumors and specifically in neuroectodermal and breast cancers.On the basis of markers displayed on the cell surface of cancer cells, the fractions are formed and these are also found to generate a sub-class that has more enhanced abilities compared to the normal cancer cell population. This shows high growth rate in case of immune deficient mice model[16].

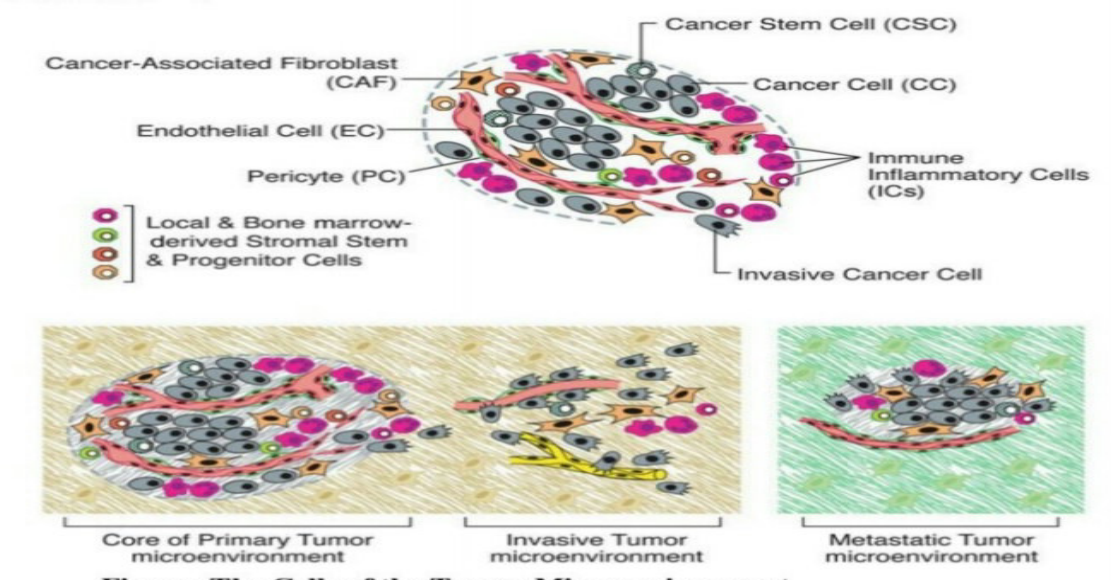

Figure- 3 the cells of the tumor Microenvironment

Immune inflammatory cells

These sub-class of cancer cells are rarely seen with identical profile that justify their designation of cancer stem cells that vary in their genetic material hence much more difficult to identify and target easily.The variability of cancer stem cells is not yet very cleared with solid tumors because of their property of changing genetic makeup from one cell to another cancer cell. There are somecancer cells that are not well differentiated transit amplifying cells and those cells are termed as progenitor cells. These cells are not fully differentiated because these possess more likely to that of stem cells and have undergone only initial phase of oncogenic transformation.

For cancer stem cells to produce their differentiated derivatives as spawn. Firstly there is need of formation of primary tumors. The neoplastic cancer stem cells also form a bulk of these differentiate cancer cells.During constant increase of distinct classes of neoplastic stem cells, it remains stable whenthere is inception and multiple progressions subsequently in case of tumors. And, produce thecancer stem cells that are found in fully developed tumors that are main threat to patient's life andvery rarely have effect of any treatment therapy on them [17].Hence, it is received as an outcome of one of the finding of researchers that these cancer stems are self-renewal in nature and have association with antigenic phenotypes with that of normal as well as cancer stem cells.

Stem and progenitor cells of tumor stroma

The self-renewal property of cancer stem cells helps cancer cells to physically differentiate from primary cancer cells and this property is very crucial during the subsequent formation of cloned expansion at dissemination site.

For creation and maintenance of the cancer stem cells, it is important that there should be release of heterotype signals basically triggered by activated inflamed stroma. It is reported during a study that at the time of xenotransplantation in mice that there is increase in the population of human tumors that have sub population as the property of cancer stem cells. This can only be explained by their tumor generation capabilities.

As a possible outcome, it is needed to perform phenotypic plasticity operation within the tumor that may generate a two directional interconversion CSCs and healthy cells, which possibly provide outcome that results in dynamic variability in the relative abundance of cancer stem cells. This is very helpful in decreasing their rate of prevalence, hence not able to withstand complexities.This is the proof that various tumor types suggesting high resistance of cancer stem cells against the frequent chemotherapeutic treatments. Their persistence is very helpful in understanding the reoccurrence of this inevitable disease.

This is also helpful in reduction of bulk of solid human tumors through different types of chemotherapy and radiation therapy. Many tumor cells persist in the body several years anddecades

even after successful chemo radiation therapy or surgical resection.These left forms like debries of these cancer cells may suddenly get erupted and have a severe threat to patient's life.

Hence, they become more resistance and produce double threat against therapeutic treatment available and have the ability of regeneration of tumors, if the therapy is halted at any phase during the course of treatment [18]

Recently several reports indicated that glioblastoma cells have ability that they can differentiate into endothelial-like cells that results in substitution of host derived endothelial cells that results in the formation of nano vasculature associated with tumor. Under observation it is found that presence of stromal support for some tumors by the induction of their own tumor cells that results in initiation of different types of metamorphosis to generate various types of stromal cells rather waiting for host cells to produce desired functions.It is discovered from a study that biologic plasticity and cancer stem cells in tumor tells that a single genetic homogeneous population with a tumor will never can be of phenotypic heterogenous because the cells are present in distinct differentiation states,However, it can also be seen that it is equally important that derivation of phenotypic source variability from genetic heterogeneity into the tumor only that helps in the accumulation of tumor progression rate. And hence, show increase in the genetic instability in the body and needs to be operated the later stages of progression of disease that results in diversification of the process and start generation of sub populations that are produced much more rapidly than the rate at which these are getting killed or eliminated. This problem can be overcome upto some extent by the process genetic sequencing that is possible practical at industrial scale as there are recent advancements in sequencing technology of DNA and RNA. This may be helpful in reflection of long term diversity in recognizing the heterogeneity within the particular human tumors individually [19].

Metastasis of cancer

A graphic depiction relating networking of microenvironment signal interactions still has to be accomplished because of large amount of signaling molecules having remarkable complexity that is critically important to the pathogenesis of cancer. In the figure depicted below, showing hints for such interactions. These fully established examples justify the exemplification of this signaling network of remarkable complexity that is critically important in the pathogenesis of tumor.

There is progressive change of neoplastic and stromal cells that are present around the stromal cells during a multistep transformation process of normal cells to melanomas of higher grade. This progression of histopathological changes that must be reflecting the heterotypic signaling between stromaand parenchyma cancer cells [20]. As depicted in the figure, the depending of stepwise progression might be on back-forth reciprocal interaction between supportive stromal cells and neoplastic cells. This particular model of reciprocal heterotypic signaling might be lengthened for encompassing the final stage of multistep cancer progression i.e., metastasis.

The cancer cells that are circulating might be released from primary tumor cells leaving a tumor microenvironment that is created by the support of stroma of such tumor cells. But, during landing in a particular organ these cancerous cells encounter a naive, normal tissue microenvironment. Many signals that are heterotypic in nature shapes their phenotype and hence residing with primary tumors that may not be present at the site of dissemination and producing as strong barrier for opposing the growth of seeding tumor cells.

This logic is not applicable at all places and is only implemable in few cases of metastasis and in others as described earlier due to various reasons different tissue microenvironments already supports fresh seeding tumor cellsand these are sites permissible that are termed as "metastatic niches". It is clear from above mentioned findings that signaling interactions between supporting stromal cells and tumor cells comes into existence during the multiple tumor stage development process that complicates the goals of elucidating the cancer pathogenesis mechanism [21].

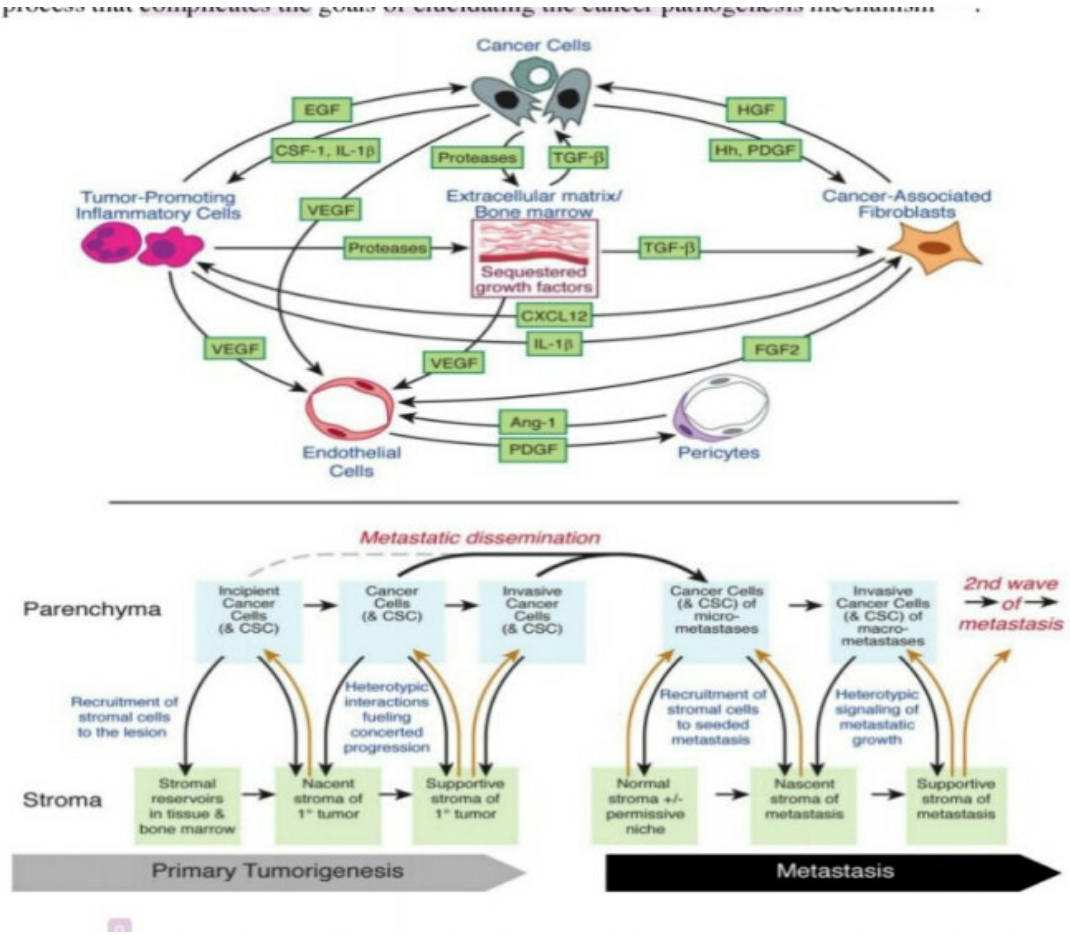

Figure-4 Signaling interactions in the tumor microenvironment during malignant Progression

Therapeutic targeting

Targeted therapies for the treatment of tumor have proven fruitful in the past three decades. These are solely mechanism-based therapies for targeting human cancer and have shown effectiveness in possessing therapeutic efficacy against human cancer. The therapies that are not fully developed or are under clinical trial phase are not considered for the treatmentpurpose. The fast-growing medical techniques and advances in medication system is very reliable for focusing targets according to their capability against different hallmarks and it is explained better in the figure below. According to a certain observation, it is observed that in each case, there is validation of particular activity to know whether it is effective against biology of cancer cells or not, if so then it should impair cancer growth and progression on its inhibition.

Specific molecular targets are engaged in a way or other way to enable specific capabilities that are directed towards specified molecular targets. Growing experimental proofs from interpretation of history states that the capabilities of hallmarks are partially regulated by signaling pathways [22]. Consequently, when there is inhibition of main pathway of tumor by targeted therapeutics, it is not mandatory that it completely wave off the capability of hallmark and resulting in survival of few tumor cells to survive till they are not burden under pressure enforced by cancertherapy. Renewed cancer growth, clinical relapse and functional capabilities can be achieved by mutation, remodeling microenvironment of stromal cells and epigenetic reprogramming.

There is still scope of establishment of applicability to human tumors. It can be easily understood from an example that there is deployment drugs that induce apoptosis that are responsible for inducing cancerous cells to a hyperactive signaling of mitogenic cells that have authority to compensate the trigger from prior attrition rate during the treatment.By incorporation of functional hallmark capabilities conception that

might be considered for development of drugs and treatment protocol design will be benefitted ad these all process is also supported by biochemical pathways. Hence, there is scope of specified co-targeting of multiples cores, emerging capabilities ofhallmark, enabling their characteristics in guiding mechanism combinations that provide durableand many effective targeted therapies for tumors in human population. The hallmarks of tumor can be understood with time that these are considered as integral part of most of the types of cancers. We are looking forward in the coming future to have a significant advancement in a better understanding of the metastasis and invasion process. And also, the aerobic glycolysis role in the malignant growth of tumors can be described more accurately in the near future [23,24].

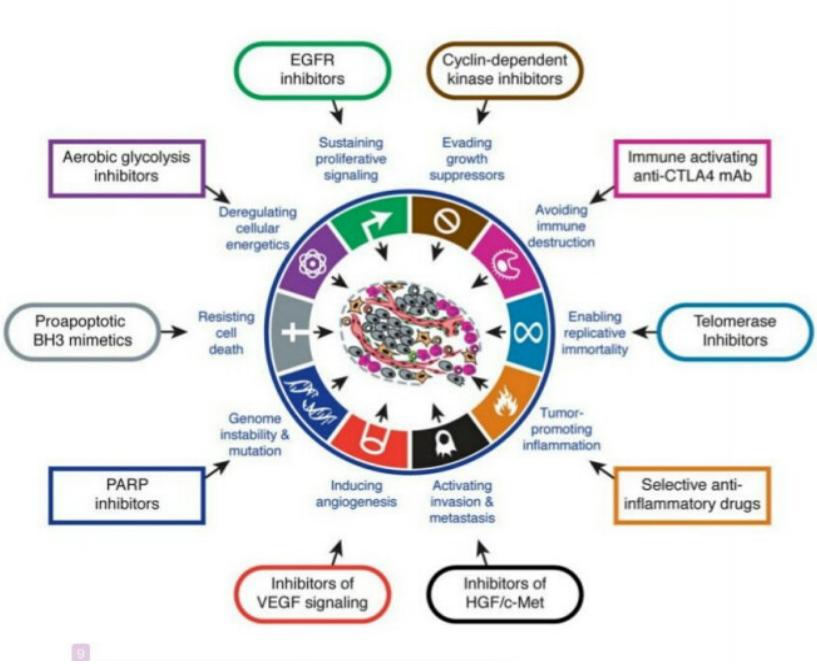

Figure 5- Therapeutic targeting of the hallmarks of cancer

Repurposing drugs as cancer therapeutics

The traditional process of designing and discovering of new chemical entities for clinical use is often a strenuous and expensive endeavor. It has been estimated that the de novo development of most drugs takes 10-17 years and costs over $800 million. A comprehensive and industry-wide analysis conducted by Paul et al. determined that the average drug development time is 135 years and an estimated $1 8 billion is required to bring new chemical entities to market. Drug repurposing and drug repositioning has the potential to reduce the time and cost required to obtain approval for new clinical indications, which can support a relatively rapid bench-to-bedside transition [25].

Drug repurposing is believed to shorten the time of drug development from an estimated 10-17 years to 3-12 years while reducing costs by approximately 40%. The main sources for cost reductions in drug repurposing are derived from the fact that the pharmacodynamic and pharmacokinetic and also the toxicity profiles are well established for these previously FDA approved drugs. Repurposing of the antidiabetic drug metformin for the treatment of several cancers including breast, ovarian, endometrial, and uterine cancer has progressed in clinical trials.Similarly, aspirin has been found to exert a small effect in reducing incidence of metastatic cancer Repurposed drugs, especially when generic versions are available, have the potential to greatly reduce costs incurred by cancer patients. The National Center for Health Statistics recently reported a third of uninsured patients did not take their medications as prescribed in order to reduce costs, which underlines the problem that the financial burden to patients has important clinical implications[26].Numerous studies suggest that

targeted therapies selectively blocking individual enzymes or single pathways seldom result in effective cancer treatment while FDA approved less selective systemic therapies (c.g. DNA damaging agents) often damage nonmalignant tissue leading to toxicity. Thus, there is an increase need of drugs that can bind with promiscuity and modulate multiple targets, yet have minimal effects on normal cells [27].

Metformin

P. Nowak-sliwinskact metformin, the recent cohort studies with over "forty-seven thousand participants designed to degree those biases revealed that long-term use of metformin appeared to be associated with the reduced risk of colorectal cancer." To administrated metformin in the population significantly suppressed the no. of intestinal polyps formed in the both models, not only urine, but also in rats.

Celecoxib and rofexcoxib

P. Nowak-sliwinska celecoxib and rolexcoxibcelecoxib and rofexcoxib. The use of cox-2 inhibitors celecoxib for "CRC was reported in several clinical trials. A group of 77 patients with prevention was familial adenomatous polyposis (FAP) treated with celecoxib (400 mg daily twice for 6 month)" led to significant reduction in the no. of colorectal polyps [28].

Mesalamine

P. Nowak sliwinska mesalamine in several studies mesalamine was, reported to decrease the growth and survival of CRC cells various signaling pathways moreover, Finact al reported that mesalamine enhanced. CRC cells anoikic, a form of programed cell death triggered by the loss of anchorage to the extracellular matrix [29].

Epirubicin

P. Nowak sliwinska ploskeret, showed that a fraction of MCRC patients resistance to "oxaliplatin exhibited DNA TOPOISOMERASE 2-ageneamplificant". Epirubicin a 4epimer of the anthracycline antibiotic doxorubicin actually targets TOP2a and thus interferes with the synthesis of DNA through intercalation being most active in s-phase of the cell cycle [30].

Acetaminophen

Web acetaminophen there was no association between regular use of acetaminophen and endometrial cancer risk in several studies with the available information. Stratification by BMI suggested an inverse association among overweight women but no association can be seen with women having normal weight[30].

Methyltransferase

Y Niu "methyltransferase: the function of m'a modification methyltransferase in human cancer. METTL3 was the major RNA N-adenosine methyltransferase, which was reported to be closely associated with the genesis and development of cancer chenet.al showed that METTL3 war significantly upregulated in human hepatocellular carcinoma solid tumors knockdowm or knockout of METTL3 would drastically reduce HCC proliferation migration, colony formation invitro and suppress HCC progression[31].

Orlistat

Paulmurugan is orlisat is a hydrophobic drug and its bioavailability in the current ant obesity therapeutic regimen of 60 and 120 mg daily dose has been estimated to be less than 1%; therefore, hypothesized that by increasing orlistat solubility after loading it's in NPs." It would be possible toenhance its bioavailability and it may in turned to reduce the orlistat dose needed for both ant obesity and repurposed anticancer therapeutic applications.

Succinimide

AD A Qahtani succinimide a succinimide-activatedPEG derivative has been used to PEGylate the amino groups of lysine residues of xanthine Soxide, which mediates anticancer activity because of its ability to generate cytotoxic reactive oxygen species [32, 33].

Flurouracil

P. Chandran development of "chitosan loaded 5 flurorouracil" nanoparticles, to minimize the toxicity of these powerfulpharmaceutical on healthy cells and concluded that the formulated chitosan nanoparticles improved localization of drug at colon region, which was followed by a sustained release mechanism over a period of 24 hrs, this can also be leaded to a greater vol. of drug is localized in the colorectal cancer [34, 35].

ONIVYDE+5-FU."

P Chandran ONIVYDE+5-FU" it demonstrated an improvement in median overall survival since, the improvement in median overall survival means patient receiving ONIVYDE+5-FU, had a greater, chance of living longer when compared with 5 fu, group alone[36, 37].

Doxorubicin

Chen he reported a unique architecture, cation polymeric Nano capsule, which had well- defined

covalently stabilized biodegradable structures can function as a potentially universal and safe therapeutic nanocarrier for co delivery of doxorubicin and siRNA targeting interleukin-8.[38].

Paclitaxel

Tarantula reported the co-delivery of siRNA targeting BCL 2 MRP-1 and Dox/paclitaxel (TAX) using LHRH (luteining hormone-releasinghormone) conjugated nanostructured lipid carries (NLCS) for lung cancer in vivo. Here the lipid phase consisted of pectoral ATOS SQUALENE and soybean phosphatidyl- choline, whereas the aqueous phase was composed of "tween-80, 1.2. dioleoyl 3- trimethylammonium - propane and 1.2di- stearoyl sn-glycero3. phosphoehtanolamine-n (carboxy (polyethylene gly-col)2000). Preferential accumulation of siRNA/DOX in the lung cancer cells was observed in vivo using a mouse orthotopic model of human lung cancer via inhalation administrated". The tumor size in animals treated with LHRH-conjugated. NLCS loaded with both Bcl 2-siRNA and TAX shrank down to 2.6+3.0mm after 24 days treatment [39].

Quinacrine

D.B. OIENrecent reports suggest quinacrine may inhibit cancer cell growth through multiple mechanisms including regulating autophagy, FACT (facilitates chromatin transcription) chromatin trapping and the DNA repair process. Additional reports also suggest quinacrine is effective against chemo resistant gynecologic cancer [40].

Levofloxacin

Yu suggested that levofloxacin exerts antiproliferative andapoptotic effect in breast cancer cells through inhibition of mitochondrialbiogenesis induced by the deactivation of p13/akt/MTOR and MAPR/ERK pathways, which was confirmed by song et al. reported that levofloxacin exerts antiproliferative and apoptotic effect in lung cancer cells via upregulation of ROS. Mitochondrial superoxide hydrogen and oxidative stress makers (HEL and 4-hne) [42].

Mechanism of action drugs used for cancer treatment

Metformin

It acts directly on cancer causing cells by directly terminating the growth promoting factors like mTOR, SREBP-1 and FASN. It is also helpful in activation of tumor suppressors. This directly effects through both AMPK-dependent and independent mechanism [43].

Celecoxib

It is a COX-2 inhibitor for isoform of cyclooxygenase; it also inhibits the transformation of arachidonic acid to prostaglandin precursor. It also possesses anti-inflammatory and analgesic property as well. NSAIDs like aspirin, ibuprofen is helpful in inhibiting both COX-1 & 2[44].

Rofecoxib

It selectively inhibits COX-2 enzymes that plays a major role in reducing the pain associated with cancer and other inflammation. Unlikely, that of non-selective NSAIDs, it does not eliminate platelet aggregation [45].

Prostaglandins

Lipoxygenase and cyclooxygenase are responsible for the production of prostaglandins. In case of ulcerative colitis or cancer, these enzymes are over active in some of the individuals. Mesalamine is helpful in blocking the activity of the two above mentioned enzymes lipoxygenase and cyclooxygenase and therefore results in reduced production of prostaglandins and thus helpful in reducing the pain and associated symptoms with ulcerative colitis [46].

Paracetamol

It is also used for the management of pain in cancer during surgery. It is given in combination with opioids that are helpful in reducing the pain during cancer. It isadministered through oral route or rectally, it can also be injected to veins and its effect last for 2-4 hours[47].

Methyltransferase

It is helpful in methylation of cancer suppressor genes a vital mechanism contributing in the reaction mechanism of DNA methyl transferees that is basis of formation of covalent intermediate between target base and enzymes that is helpful in success of this class of drugs targeted against DNA methylation 7. Orlistat. It works by inhibiting pancreatic and gastric lipases and also the enzyme that isresponsible for breaking of triglycerides in the small intestine. Recently it is found that ithas some of its other vital functions such as inhibition of thioesterase domain of fatty acid synthase and proliferation of tumor cells except normal cells [48].

Succinimide

A succinimide activated derivative has been used to PEGylated the amino groups by lysine residues of xanthine oxide, which mediates anti-cancer activity because of its potency of formation of cytotoxic reactive oxygen species (ROS). 9. ONIVYDE - It is a Topoisomerase-I inhibitor that is encapsulated in a lipid bilayer. Its active metabolite SN-38 reversibly binds to the DNA complex of Topoisomerase-I and helps in prevention of re-ligation of single strand breaks, resulting in exposure of time dependent double strand DNA damage and cell death of affected cells[50].

Quinacrine

It is a small molecule ie, derivative of 9-amino acridine that also shows its activity against cancer cells and simultaneously helpful in suppressing the nuclear factor - kB and activates p53 signaling.

Levofloxacin

It a class of antibiotic drugs that has been approved by FDA and is also helpful in the treatment of breast cancer. This is done so by inhibiting the process of proliferation and induction of apoptosis in breast cancer cell lines and does not affect normal cells. It shows synergistic affect with conventional chemotherapy drugs in two independent in vivo breast xenograph mouse models. It acts by inhibition of biogenesis of mitochondria and results in decreased mitochondrial respiration, ATP and membrane potential [51].

Sunitinib

It is a multikinase inhibitor approved by the FDA and/or EMA for GIST, renal cell carcinoma (RCC) and pancreatic cancer. Independent of targeting specific oncoproteins (eg, mutant KIT in GIST), sunitinib was designed for dual inhibition of VEGFR and PDGFR RTKs which are critical for tumor neoangiogenesis and combined inhibition of which in the tumor microenvironment produces potent antitumor effects in various cancers [51].

Sorafenib

Inhibits multiple kinases, including VEGFRS, PDGFRB, and exhibits potent antiangiogenic and antitumor effects, although it was primarily designed to target RAFI. Sorafenib is approved for RCC, hepatocellular carcinoma, and thyroid cancer. [52]

Cabozantinib

It suppresses metastasis, angiogenesis and oncogenesis by inhibiting receptor tyrosine kinases. It also inhibits specific receptor kinases such as VEGFR-1, 2, 3. RET. MET and TIE-2.

Dasatinib

It binds to and inhibit the growth promoting activities of these kinases. It is an oral dual BCR/ABL and Src family tyrosine kinase inhibitor approved for use in patients KIT, TRKB, FLT3, AXL. with chronic myelogenous leukemia. It's main target are BCRABI, SRC, Ephrins and GFR

Foretinib

It is a multi-kinase inhibitor of MET and VEGFR$-" that inhibits the growth of gastric cancer cell lines by blocking inter-receptor tyrosine kinase network".

Certinib

It exerts its therapeutic. action by inhibiting autophosphorylation of ALK, ALK-mediated phosphorylation of the of the downstream signaling protein 'STAT3 and proliferation of ALK-dependent cancer cells [53].

Itraconazole

It acts on numerous pathways necessary for angiogenesis. It inhibits - vascular endothelial growth factor signaling by preventing VEGF binding to VEGF-2. thereby reducing endothelial cell proliferation [54].

Disulfiram

It is a clinically used as an anti-alcoholism drug that induces apoptotic cell death in breast cancer cultures and xenografts via inhibition of the proteasome activity.

Sulfasalazine

It is a potent xCT inhibitor that plays an important role in maintaining the GSH levels, impaired the ROS defense system and increased the therapeutic efficacy of anticancer therapies[55].

Artemisinin

Artemisinin and its analogues are naturally known for its anti-malarial activity but it has also shown potent anticancer activity. In primary cancer cultures and cell lines, their anticancer actions were by inhibiting cancer proliferation angiogenesis and also by metastasis [56].

Chloroquine

Uptill now, inhibition of the late stage of autophagy was thought to be the major mechanism of chloroquine-mediated cancer cells death. But

according to recent research it is found that autophagy-inhibiting activities of chloroquine are dispensable for its ability to suppress tumor cells growth [57].

Imatinib

It is a tyrosine kinase inhibitor. It is also known as "magical bullet" when it revolutionized the treatment of chronic myeloid leukemia in the year 2001. It mainly acts by restricting the Ber-Abl tyrosine kinase. This cither slows down the growth of cancer cells or results in programmed cell death of certain types of cancer cells [58].

Midostaurin

It shows its therapeutic efficacy when given in combination therapy for patients undergoing chemotherapy. Its major active metabolites CGP62221 & CGP52421 inhibit the activity of protein kinase C. alpha, VEGFR2, KIT, PDGFR.

Erlotinib

Its mechanism of action is not fully characterized. It inhibits the intercellular phosphorylation of tyrosine kinase associated with the epidermal growth factor ie..expressed on the cell surface of normal cells and cancer cells [59].

Ibrutinib

It is found to reduce chronic lymphocytic leukemia cell chemotaxis towards the chemokines CXCL12 and CXCL 13 and it also inhibits cellular adhesion following stimulation at the B-cell receptor.[60]

Crizotinib

It inhibits the hepatocyte growth factor receptor tyrosine kinase that is involved in the oncogenesis of a number of other histological forms of malignant neoplasms.

Midostaurin

It is therapeutically beneficial as a combination therapy for patients undergoing chemotherapy. Its active metabolites CGP62221 and CGP52421 inhibit the activity of protein kinase C. alpha. VEGFR2, PDGFR and mutant FLT3 tyrosine kinases

Axitinib

It prevents the progression of cancer by inhibiting angiogenesis and blocking tumor growth. Axitinib selectively blocks the tyrosine kinase receptors VEGFR-1 2 and 3.

Zardaverine

A potent and selective anti-tumoral effect on sensitive HCC cells was demonstrated also for Zardaverine, a dual-selective PDE3/4 inhibitor. The effect was consequent to blockage of the cell cycle in the GO/G1 phase, to the dysregulation of important proteins, including Cdk2. Cdk4.Cdk6, Cyclin E, p21 and Rb and to the induction of apoptosis through cleavage of caspase-3, 8 and 9.

Anagrelide

It works by inhibiting the maturation of platelets from megakaryocytes. The exact mechanism of action is unclear, although it is known to be a phosphodiesterase inhibitor. It is a potent inhibitor of phosphodiesterase-II. It inhibits PDE-3 and phospholipase A2 [61, 62, and 63].

Tepoxaline

Tepoxalin showed an intriguing association with expression of ABCBI. which encodes p-glycoprotein (MDRI). Whereas for most oncology drugs, including taxanes and vinca alkaloids, high ABCBI expression is associated with drug resistance, high

C Expression of ABC is predictive of sensitivity to tepoxalin.

Its mode of action is due to rapid conversion into cytosine arabinoside triphosphate, which damage DNA when the cell cycle holds in the synthesis of DNA. It is first drug of the series of cancer drugs that altered the sugar component of nucleosides whereas other cancer drugs modify the base of the drug.

Atorvastatin

The HMG-CoA reductase inhibitors, statins, have been used as lipid lowering drugs for decades and several epidemiological studies suggested statins usage correlates with a decreased incidence of cancer specific mortality in patients. The lipophilic atorvastatin decreases cancer cell proliferation and in vitro survival

Ivermectin

Ivermectin inhibits the P-glycoprotein pump. That induces a multi-drugphenotype in the cancer cell and it also acts as an ionophore&upregulates chloride channels to generate apoptosis and osmotic cell death [64-66].

Cancer drug delivery

Metformin

Metformin hydrochloride (Met) encapsulated liposomal vesides for enhanced therapeutic outcomes at reduced doses against breast cancer. Liposomal Met was prepared using thin-film hydration through various loading methods: passive loading, active loading, and drug loaded lipid film.

The drug-loaded film method exhibited maximum entrapment efficiency (-65%) as compared to active (-25%) and d passive loading (-5%) prepared Met-loaded liposomes. The therapeutic efficacy of these optimized liposomes was evaluated for cellular uptake. Cytotoxicity, demonstrated inhibition of metastatic activity. and apoptosis-inducing activity. Results significantly cantly superior activity of positively charged liposomes resulting in reduced ICs, values, minimal cell migration activity, reduced colony formation, and profound apoptosis induced activity in breast cancer cells as compared to Metformin.

Celecoxib

Particle size of celecoxib influences the content uniformity, dissolution andbioavailability of the product.Thetmax of celecoxib is about three hours after oral administration, Rapid onset of action is necessary to provide fast pain relief in the treatment of acute pain. Therefore, it is necessary to enlar to enhance the aqueous solubility and dissolution rate of celecoxib to obtain faster onset of action to minimize the variability in absorption and improve its overall oral bioavailability. This can be achieved by formulating the drug in lipid-based systems. Among the lipid-based systems.

Self-microemulsifying drug delivery system (SMEDDS)

SMEDDSis a promisingtechnology to improve the rate and extent of the absorption of poorly water-soluble drugs. Attempt was made to improve the dissolution of poorly soluble d Rofecoxib was microencapsulated with developed cross-linked starch, using Solvent Evaporation Technique. The prepared microspheres were white, free-flowing, and almost spherical in shape. drug. Rofecoxib, The efficiency of the cross-linked starch polymers was evaluated by using different tests like extent of cross-linking of starch by lodine reaction with it, IR interpretation, Mean particle size, Water regain capacity. Action of a-amylase on native starch and cross-linked starch, Gel filtration chromatography. In vitro drug release. Extent of cross linked starch was found to be highest [67-70].

Rofecoxib

An attempt was made to improve the dissolution of poorly soluble drug, rofecoxib was encapsulated with developed cross linked starch, using solvent Evaporation technique . The prepared microspheres were white, free flowing, and almost spherical in shape. The efficiency of cross linked starch by iodine reaction with it, IR interpretation , mean particle size , water regain capacity, action of α-amylase on native starch, gel filtration, chromatography, In vitro drug release.

Prostaglandins

Antitumor PGs are actively incorporated through cell membrane and control geneexpression. Very recent studies clarified that P53 independent expression of p21 and gadd 45, Activation of PPARy are involved in antitumor mechanism of these PGs. At the low concentration,these PGs exhibit physiological or pathological activity such as osteoblast calcification, promotion of colon cancer cell proliferation Lipid microspheres and Lipiodol formulation were examined as dosage form of the PGs und lipid microspheres were selected for further study. Lipo TEI-9826 exhibited marked antitumor effect in several animal models including CDDP resistant nude mice fever. It is typically used for mild to moderate pain relief. In combination with opioid pain medication, paracetamol is also used for more severe pain such as cancer pain and pain aier surgery [71-73].

Paracetamol

Paracetamol also known as acetaminophen is a medication used to treat pain and it is typically used either by mouth or rectally but is also available intravenously. (Effects lastbetween two and four hours. Paracetamol loaded Eudragit S100 nanoparticles were preparedby salting out technique using ethanol as a solvent.

Methyltransferase

DNA methyltransferase 1 (DNMTI) promotes DNA methylation to maintain cancer drug resistance Tested the efficacy of Decitabinet DAC).loaded nanogels in doxorubicin resistant breast cancer cells DAC-resistant melanoma cells and leukemia cells DAC in nanogel sustained DNMTI depletion, prolonged cell arrest in the G2/M cell cycle phase, and significantly enhanced antiproliferative effect of DAC. The efficacy of DAC-loaded nanogels was more significant in resistant than sensitive cells. Our data suggest that effective delivery of DAC and prolonged DNMTI depletion are critical to overcoming drug resistance[74].

Orlistat

Delivery of orlistat via PLGA-PEG-NPs reduced its Iso compared with free orlistat Combined treatment of orlistat-loaded NPs and doxorubicin or antisense-miR-21-loaded NPs

significantly enhanced apoptotic effect compared with independent doxorubicin, anti-miR-21 loaded NPs orlistat-loaded NPs or free orlistat treatments

Tamoxifen

The mucopermeating, stabilizing and targeting capability of the PAP-HA-sS-LCA polymeric excipient was investigated by manufacturing tamoxifen (TMX) loaded self- napoemulsifying drug delivery system (SNEDDS), TMX loaded PAP-HA--LCA incorporated SNEDDS (TMX-PAP-HA-ss-LCA SNEDDS) were characterized for their surface chemistry. Drugrelease, permeation enhancement, biocompatibility and antitumor activity.

Doxorubicin

Doxorubicin-loaded, enzymatically activatable nanoparticles of less than 100 nmwere prepared successfully by nanoprecipitation of copolymer blends. These nanoparticles were found to be suitable as controlled drug delivery systems and contrast agents for imaging of cancer cells.

Quinacrine

Therapeutic efficacy of the quinacrine formulations was tested in different NSCLC cells. Mechanism of higher anti-proliferation was evaluated by studying cell cycle profile, apoptosis and molecular markers involved in the progression of lung cancer. BSA coated QA nanoparticles demonstrated good aerosolization potential with a mass median aerodynamic diameter of significantly less than 5 um. Nanoparticles also demonstrated improved therapeutic efficacy against NSCLC cells in terms of low IQ values, cell cycle arrest at G2/M phase and autophagy inhibition leading to increased apoptosis [75,76].

Hydroxycamptothecin

Zhang et al. reported PEGylated NLCs to improve the stability of lactone form of 10-hydroxycamptothecin (HCPT), to enhance its circulation time, and anti-tumor activity (Zhang et al., 2008). They formulated PEGylated NLCS by melt-emulsification and homogenization method. The dispersed oil phase containing drug was added into an aqueous solution of PEG. In order to improve the targeting potential by binding specifically to the cancer cell receptors, NLCs were surface-engineered with different high affinity ligand molecules like NAG, transferrin (T). hyaluronic acid (HA), and bombesin for the treatment of lung cancer.

Chloroquine

To investigate the advantages of the autophagy inhibitor enhanced drug delivery by the PEG-1-PLGA micelles in vivo, we developed a xenograft tumor model in SCID mice, which were then treated by intraperitoneal injections of the DTX-loaded PEGD-PLGA micelles without and with combination of Chloroquine (CO) respectively every 3 days for six consecutive cycles. The tumor growth of the mice treated by the DTX, DTX-loaded PEG--PIGA micelles with or without combination of CQ were both found suppressed in comparison with those treated by the physiological saline group.

Atorvastatin

Present work is an attempt to improve tumor targeting of atorvastatin by Incorporating in nanostructured lipid carriers (NLCs) and studying its anticancer activity on MCF7 cell lines. NLCs of atorvastatin were formulated by high speed homogenization followed by probe sonication method. The optimized batch of NLCS had a mean size of 130.02 +3.1 nm and entrapment efficiency of 90.42 +3.7%. The in vitro drug release study by dialysis method indicated that drug entrapped in the NLCs remains entrapped at acidic pH as well as in phosphate buffer of pH 74 for a prolonged period of time as compared to plain drug.

Cytarabine

To elucidate the tumoricidal role of CYT-loaded CCIONPs next we tested the tumorinhibition efficiency in HepG2 cells under the exposure of CCIONPS. The results showed that various concentrations (25.50.100g) of CCIONPs significantly halted the colony formation capacity. In this study, cells were cultured in complete medium with or without various concentrations of CCIONPs for 6 days. The, results showed that even 25 pg/ml. CONCEPTS greatly suppressed not only the formation of tumor spheres but also reduced its efficiency. In addition, treatment with 50 and 100 pg/mL of CCIONPs resulted in more than 40% reduction in clonogenicity and tumor sphere formation [77-79].

Cisplatin

Poly(vinyl pyrrolidone, stabilized fluorescent red copper nanoclusters can be convertedinto hydrogel nanocarriers through crosslinking with poly(vinyl alcohol) to deliver the anticancer drug cisplatin (CP) to cervical cancer cells (Hela), thereby inducing apoptotic cell death. The high encapsulating efficiency is attributed to molecule

loading on the surface and inside the hydrogel particle, followed by strong interactions using various functionalities, such as COOH. The significant decrease in cell viability in the presence of drug-loaded carriers as opposed to free drug molecules reveals the combination of Cu NC-hydrogel composites and CP as a potential material for the design of new chemotherapeutic agents.

Erlotinib

The aim of this study was to develop PEGylation liposomes formulations of erlotiniband evaluate their characteristics, stability, and release characteristics. The average particle sizes and entrapment efficiency of PEGylationerlotinib liposomes are 102.4+3.1 nm and 85.318%, respectively. Transmission electron microscopy images showed that the liposomes dispersed well with a uniform shape and no changes during the storage. In vitro anticancer activity assay showed that the blank liposomes had lower cellular cytotoxicity and that the cellular cytotoxicity of erlotinib liposomes increased significantly under the same incubation condition, which should contribute to the increase in intracellular drug concentration by the transportation of liposomes. The two liposomes of erlotinib (with and without PEGylation) exhibited similar cellular cytotoxicity with no significantly different concentrations, Pharmacokinetic results indicated that erlotinib-loaded PEGylation liposomes can significantly change the pharmacokinetic behavior of drugs and improve the drug bioavailability by nearly 2 times compared to ordinary liposomes 1800 [80,81].

Imatinib

Imatinib-loaded chitosan-modified magnetic nanoparticles were prepared as a pH Sensitive system for targeted delivery of drug to tumor sites by applying a magnetic field. The proposed magnetic nanoparticles were prepared through modification of magnetic Fe:0 nanoparticles with chitosan and Imatinib. Thermal stability of the prepared particles was investigated and their efficiency of drug loading and release profile were evaluated. The results demonstrated that Fe,0.@CS acts as a pH responsive nanocarrier in releasing the loaded Imatinib molecules. Furthermore, the Fe.O @Cs/Imatinib nanoparticles displayed cytotoxic effect against MCF-7 breast cancer cells Results of this study can provide new insights in the development of pH responsive targeted drug delivery systems to overcome the side effects of conventional chemotherapy[82].

Aspirin

"In this study, delivery vehicles comprised of microvesicles loaded with engineeredminicircle (MC) DNA that encodes prodrug converting enzymes were developed as a cancer therapy in mammary carcinoma models. In the study it is demonstrated that MCs can be loaded into shed microvesicles with greater efficiency than their parental plasmid counterparts and that microvesicle-mediated MC delivery led to significantly higher and more prolonged transgene expression in recipient cells than microvesicles loaded with the parental plasmid. Microvesicles loaded with MCs encoding a thymidine kinase (TK)/nitroreductase (NTR) fusion protein produced prolonged TK-NTR expression in mammary carcinoma cells. In vivo delivery of TK-NTR and administration of prodrugs led to the effective killing of both targeted cells and surrounding tumor cells via TK-NTR-mediated conversion of co-delivered prodrugs into active cytotoxic agents 14 [83].

Hydroxyurea

It is clear that cancer is one of the most mortal diseases in the world and the most prevalent among women is breast cancer. As hydroxyurea (HU) a drug which is used inchemotherapy has many adverse effects in long-term despite of its therapeutic properties, we made use of nano drug delivery technology in order to reduce adverse effects and increase therapeutic index. Thus, liposomation is a novel way in drug delivery systems. In this study a mixture of phosphatidylcholine and cholesterol was mixed and HU was added to the resultant mixture. The mean diameter of the nano liposomal HU measured with the Zeta Sizer device (equal to 402.5 nm) and its encapsulation efficiency was 70.8 %, The pattern of drug release from nanoliposomes has been studied and the results showed that the drug release of nano liposomaldrug within 28 h was equal to 25.85 %. This study showed that the cytotoxicity effect of nano liposome drug is more than that of the standard drug [84].

Disulfiram

Disulfiram (DSE) an alcohol-a version drug has been explored for cancer treatment. Copper diethyldithiocarbamate (Cu(DDC) complex formed by DSF and copper ions is a major active ingredient for its anticancer activity. In this study, we developed a facile stabilized metal ion ligand

complex (SMILE) method to prepare Cu(DDC); nanoparticles (NPU).The SMILE method could prepare Cu(DDC), NP. The optimized formulations demonstrated excellent drug-loading efficiency (close to 100%), high drug concentrations (increased drug concentration by over 200 fold compared to the traditional micelle formulation), and an optimal particle size in the sub-100 nm range, Cu(DDC), NPs exhibited outstanding stability in serum for 72 h and can also be stored at room temperature for at least 1 month. The anticancer effects of Cu(DDC); NP formulations were determined by multiple assays including colony-forming assay, calcine-AM propidium iodide staining, and others. Cu(DDC): NPS showed excellent activity against drug-resistant prostate cancer cells and other cancer cells with a half-maximal inhibitory concentration (ICs) of around 100nm. Our study also demonstrated that Cu(DDC); NPs induced cell death in drug-resistant prostate cancer cells (DU145-TXR) through paraptosis, which is a non-apoptotic cell death[85].

Ursolic Acid

De Araújo Lopes developed UA-loaded liposomes which composed of dioleoylphosphatidylethanolamine (DOPE), cholesteryl hemi succinate(CHEMS). Distearoylphosphatidylethanolamine-polyethylene glycol (DSPE-PEG) 2000. Liposome is the well-studied nanocarriers which composed of phospholipids and cholesterol molecules. In comparison with free drug, the liposomal drug possesses several attractive features such as controlled release, reduced toxicity, excellent stability, targeted delivery, increased solubility, higher cellular uptake, and multiple routes of administration. The obtained liposome with an and average diameter of 191.1 nm, which was benefit for drug accumulation into tumor tissues. Additionally, due to the strong interaction between UA and phospholipids in the liposome bilayer, the characteristics of liposomes remained unchanged for 60 days (86,87).

Gemcitabine

Local stent-based drug delivery has been tested using an effective anti-cancer drug.gemcitabine, but the release from the stent-coated polyurethane films is often too fast and the drug is depleted from the coated film virtually in a day. To moderate the drug release from a polyurethane film, a gemcitabine-incorporated polyurethane film was enveloped with a pure polyurethane film, with no drug loading, and with a silicone film by solution casting after activation of the silicone film surface with plasma treatment. The pure polyurethane barrier film was effective. Enveloping a gemcitabine-releasing polyurethane film with a homo-polymer barrier film was quite effective for moderating the initial burst of gemcitabine, thus, prolonging the release time of the drug [88,89].

CONCLUSION

Cancer remains to be a major global healthcare burden as 18.1 million new cases and 9.6 million death occurred 2018 on the basis of report from the international agency for research on cancer (IARC). Metastatic cancer or surgically non-respectable tumour show five years mortality above 90% in chronic cancer like pancreatic cancer and cytogenetically defined high risk acute myeloid leukaemia (AML) till present date aggressive cancer types has not been mainly due to therapeutic failure on another side a drug productivity cries appear in the pharmaceutical research and development area (R&D). On R&D cost productivity potentially reducing their R&D investment at least in certain area of research the increased cost of novel approved cancer therapeutic are raising the important issues on treatment cost.

The drug repurposing also helpful to those drug which are present with in the market to improve the revenue and identify new indication to extend the patient life of drug. It also helps to protect the compares from intellectual property against competitors. By the think drug repurposing will set more and more successful stage in future cancer therapeutics scenario which will be effective and useful. Since last decade cancer is successful in developing its identity as an organ whose complex approaches were difficult to detect as they have their genetic makeup completely different from that of healthy cells.

Drug repurposing is believed to shorten the time of drug development from an estimated 10-17 years to 3-12 years while reducing costs by approximately 40%. The main sources for cost reductions in drug repurposing are derived from the fact that the pharmacodynamic and pharmacokinetic and also the toxicity profiles are well established for these previously FDA approved drugs.

In a current research, it is also found that cancer cells have a property of intra-tumor heterogenecityie, formation of sub-group of cancer cells that shows more complexity in revelation of their genetic makeup. Hence, the research is still going, it is not yet confirmed that these cancer sub-cells are sub-part of all cancer cells, but it is assured that it is found as a part of most of the tumor cells. In a study it is found that these cancer stem cells can be easily identifies by their property of giving rise to new stem cells when they are inoculated in the host mice model in the laboratories.

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