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Review Article

Status of Cancer Research in India

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Burden of cancer in India is increasing day by day. Projected number of new cancer cases in 2016 is 1,219,649. This brings with it the need for research to investigate different India specific risk factors, mechanistic pathways, role of traditional herbal medicine, efficacy of different agents, comparative evaluation of me too agents etc. To evaluate the current status of cancer research in India, we have searched different databases like CTRI, clinicaltrials.gov, PubMed etc. regarding different publications on this topic from India. Number and quality of preclinical studies are very good, but the number of clinical studies published or registered are very less, compared to preclinical studies. North eastern states like Manipur, Mizoram are lagging behind in cancer research. We need infrastructure development to promote research in those states.

Keywords: Cancer; Research; Clinical; Pre-clinical; India

Introduction: Cancer Burden in India

Cancer is a major cause of morbidity, mortality and socio-economic burden in India (Sullivan *et al.*, 2014). To address the epidemiological issues in Indian population, National Cancer Registry Program (NCRP) is functioning since 1991. NCRP brought out a special concept called atlas of cancer for geographic region wise mapping of cancer. It is basically divided into hospital based and population based registry. The 2007-2011 report included 7 centers (hospital based) (National cancer registry, 2007-2011 report).

The projected number of new cancer cases by 2016 is 1,219,649 and the number of cancer cases is increasing (1,058,984 in 2011). The estimated cancer incidence was slightly greater in females. Certain types of cancer (e.g. esophagus, lung, stomach, oral and pharyngeal cancers) were higher in man while cervix and breast cancer was most important in females followed by oral, gastric and esophagus (Murthy *et al.*, 2008). Contribution of India towards global cancer burden is 7.8% and towards global cancer death is 8.33% (Saranath *et al.*, 2014).

The rising number of new cancer cases highlights the importance of cancer research in India. The necessity ranges from studies to determine the carcinogens, basic research techniques to evaluate different molecular pathways and new drugs for treatment or drug repurposition. In this context, we have reviewed the status of current cancer research in India.

To access the status of cancer research in India, we divided them into preclinical and clinical research.

Status of Preclinical Research in India

Many Indian universities, medical colleges, pharmaceutical colleges and research centers are involved in preclinical research and many of them are involved in cancer research, drug discovery and development, evaluation of etiopathology and molecular characterization of it. Few of the most explored research in cancer therapeutics are breast cancer, colorectal cancer, leukemia, brain cancer, lung cancer, cancer cervix and hepatocellular cancer. High

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quality researchis also going on in other types of cancers. Below we have discussed about progress of preclinical research in few targeted areas. Data is presented in tabular form in Table 1.

Breast Cancer

Basu *et al.* (2017) from Chittaranjan National Cancer Institute, Kolkata, evaluated the cancer chemo preventive potential of vanadium-based compound vanadium(III)-l-cysteine as an add on to cyclophosphamide in mice bearing breast adenocarcinoma cells. They showed that the combined treatment significantly reduced the tumor burden and enhanced survival by promotion of apoptosis and blocking of angiogenesis. Shavi *et al.* (2017) from Manipal college of pharmaceutical Sciences, Manipal university, Manipal in collaboration with pharmaceutical and molecular biotechnology research centre, Waterford Institute of Technology of Ireland, developed PLA microspheres which demonstrated the feasibility of employing as biodegradable depot polymeric microspheres of anastrozole for long-term treatment of breast cancer. Damineni *et al.* (2017) from Indian Institute of Science, Bangalore noticed that a good proportion of patients with lymph node positivity remain disease free for 5 years or more, while about a third of those who were lymph node negative develop distant metastasis within the same period. They found that primary breast cancers showing expression profile of TMP-28 (tripartite motif-containing protein-28) was associated with metastasis, stemness, resistance to chemotherapy and growth of tumor. Bhale *et al.* (2017) from School of Chemical Sciences (Solapur University), established the anticancer activity of extended conjugated indolyl-chalcones. Nair *et al.* (2017) from Rajiv Gandhi Centre for Biotechnology, Kerala evaluated the molecular trail of anticancer property of a novel copper carbohydrazone complex in a panel of cell lines with either wild or mutated BRCA-1 [HCC-1937 ($BRCA1^-$ /$ER\alpha^-$), MCF-7 ($BRCA1^+$ /ER^+), HCC1937/wt BRCA1, MX1 ($BRCA1^-$ /$ER\alpha^-$), MDA-MB-231 ($BRCA1^+$ /$ER\alpha^-$), MDA-MB-436 ($BRCA1^-$ /$ER\alpha^-$) cell lines]. Cu_2 (HL)(HSO_4)†·H_2O]SO_4·† 6 H_2O (CS2) was found to be the most potent as anticancer agent amongst all the agents evaluated. They further gave evidence that CS2 binds to DNA and induces DNA damage and resultant strand breaksas assessed by expression of γ-H2AX. Kumar *et al.* (2016) from Centre for Biomedical Engineering, Indian Institute of Technology Delhi, established the role of trastuzumab and folic acid conjugated redox-responsive random multiblockco-polymericnano carriers for treatment of breast cancer.

Other labs or institutes actively working in this field are Bharathiar University (Proteomics and molecular cell physiology Lab of Department of Zoology, School of Life Sciences, Coimbatore), Periyar University (Salem, Tamil Nadu), CDRI Lucknow, Central University of Kerala, (Kasaragod, Kerala), NIPER-Hyderabad (Department of Pharmacology & Toxicology), Babasaheb Bhimrao Ambedkar University (Department of Pharmaceutical Sciences, School of Biosciences and Biotechnology, Lucknow), Nirma University (Institute of Pharmacy, Ahmedabad, Gujarat), Bharathiar University (School of Life Sciences, Coimbatore, Tamil Nadu) and Pharmaceutical Nanotechnology Research Laboratory (ISF College of Pharmacy, Punjab).

Colorectal Cancer

Jyoti *et al.* (2016) from department of pharmaceutics, Chandigarh College of Pharmacy, Punjab evaluated the role of chitosan microsphere amalgamated curcumin-2-HP-β-CD complex for selective delivery to colon by oral route. In preclinical pharmacokinetic studies, this chitosan microsphere amalgamated complex of curcumin with 2-HP-β-CD enhanced colonic targeting of curcumin (8.36 times) compared to suspension of curcumin.

NF-κBis an important mediator of angiogenesis in colorectal cancer. Curcumin inhibits NF-κB. Going with this hypothesis, Rajitha *et al.* (2017) from Banasthali University (Department of Microbiology) in collaboration with Berhampur University (Odisha) and Emory University, (Georgia) evaluated the effect of curcumin and two synthetic analogues of it (UBS109 and EF31) on angiogenesis associated with colorectal cancer (HT-29 and HCT116 cell lines). Treatment by curcumin and its synthetic analogues resulted in decrease in angiogenesis (as evidenced by HUVEC tube formation, egg CAM assay, and matrigel plug assays), significant inhibition of VEGF-A synthesis and secretion and inhibition of nuclear NF-κB expression. In mice model inoculated with HT-29 and HCT116 cell xenografts, treatment by synthetic analogues of curcumin resulted in significant

Table 1: Preclinical research in various forms of cancers from Indian Institutes

Disease category	Institute	Key finding	Reference
Breast Cancer	Chittaranjan National Cancer Institute, Kolkata	Cancer chemo preventive potential of vanadium-based compound vanadium(III)-l-cysteine as an add on to cyclophosphamide	Basu *et al*. (2017)
	Manipal College of Pharmaceutical Sciences, Manipal University, Waterford Institute of Technology of Ireland	Developed PLA microspheres which demonstrated the feasibility of employing as biodegradable depot polymeric microspheres of anastrozole for long-term treatment of breast cancer	Shavi *et al.* (2017)
	Indian Institute of Science, Bangalore	Primary breast cancers showing expression profile of TMP-28 (tripartite motif-containing protein-28) was associated with metastasis, stemness, resistance to chemotherapy and growth of tumor	Damineni *et al.* (2017)
	School of Chemical Sciences (Solapur University)	Anticancer activity of extended conjugated indolyl-chalcones	Bhale *et al.* (2017)
	Rajiv Gandhi Centre for Biotechnology, Kerala	Anticancer property of a novel copper carbohydrazone complex in a panel of cell lines with either wild or mutated BRCA-1	Nair *et al.* (2017)
	Centre for Biomedical Engineering, Indian Institute of Technology Delhi	Established the role of trastuzumab and folic acid conjugated redox-responsive random multiblockco-polymericnanocarriers for treatment of breast cancer	Kumar *et al.* (2016)
Colorectal cancer	Chandigarh College of Pharmacy, Punjab	Role of chitosan microsphere amalgamated curcumin-2-HP-β-CD complex for selective delivery to colon by oral route	Jyoti *et al.* (2016)
	Banasthali university (department of microbiology) in collaboration with Berhampur University (Odisha) and Emory University, (Georgia)	Evaluated the effect of curcumin and two synthetic analogues of it (UBS109 and EF31) on angiogenesis associated with colorectal cancer (HT-29 and HCT116 cell lines)	Rajitha *et al.* (2017)
	Institute of Pharmacy (Nirma University, Ahmedabad)	Evaluated the chemopreventive effect of *L. usitatissimum* extract in colon cancer (associated with type 2 diabetes). They established the usefulness of this extract as a chemoprevention agent and this effect was found to be mediated through CDK4 inhibition	Shah *et al.* (2016)
	Yogi Vemana University (Andhra Pradesh) in collaboration with along with Pennsylvania State University	Evaluated the role of grape compounds on colon cancer stem cells	Reddivari *et al.* (2016)
	Punjab University (Chandigarh)	Fish oil has dose dependent effect upon mitochondrial impairments and it augments apoptosis and thus decreases carcinogenesis	Agnihotri *et al.* (2016)
	Punjab University (Chandigarh)	Evaluated different ratios of corn oil and fish oil in experimental colon carcinogenesis and expression of different markers like Fas, Bax, Cyt-C and Bcl-2 expression	Sharma *et al.* (2016)
Leukaemia	Christian Medical College, Vellore (Hematology department	Proteasome inhibitor bortezomib, when given in combination with arsenic trioxide for treatment of acute promyelocytic leukemia; the combination therapy successfully abolished the micro-environment-mediated resistance to arsenic trioxide	Ganesan *et al.* (2016)
	National Cancer Institute, Kolkata (department of *In vitro* Carcinogenesis and Cellular Chemotherapy)	Cu-5-SMAG is a promising anti-leukemia agent (predominant pro-apoptotic action), effect of which is not dependent upon phenotype of MDR. Cu-5-SMAG overcomes MDR in T-cell ALL by its inhibitory effect upon expression of EGFR/PI3K/Akt and by causing redox imbalance	Banerjee *et al.* (2016)
	Calcutta School of Tropical	Mechanistic scenario of aberrations of p53 pathways (classical	Chatterjee *et al.*

	Medicine	and hematopoiesis specific) in ENU (ethyl nitrosourea) model of leukemia	(2016)
Brain cancer	Banaras Hindu University Varanasi (Institute of Medical Sciences)	Demonstrated that transferrin receptor targeted Docetaxel loaded d-α-tocopherol polyethylene glycol 1000 succinate conjugated chitosan (TPGS-chitosan) nanoparticles had better cellular internalization, enhancement in relative bioavailability and cytotoxicity compared to their non-targeted counterpart	Agrawal *et al.* (2017)
	Jadavpur University (Department of Pharmaceutical Technology)	DTX-loaded nanoliposomes had better penetrability and thus it seems an important strategy to treat glioma with docetaxel	Shaw *et al.* (2017)
	Bharathiar University (Dept of Biotechnology, School of Biotechnology and Genetic Engineering) in collaboration with National Dong Hwa University, Taiwan	Evaluated the mechanism of action of HCD in brain tumor cell lines (glioma C6 and neuroblastoma N18 cell lines) and it was found that HCD induced autophagy was mediatyed via activation of ERK-1/2, p38 MAPK and ROS generation	Thiyagarajan *et al.* (2016)
	University of Madras	Demonstrated that in glioma cell lines, Connexin 30 is an important modulator of IGF-1 receptor, which has actions like down-regulation of IGFR-1 and abolition of ErK etc. Connexin 30 additionally potentiated the effect of inhibitors of IGF-R	Arun *et al.* (2016)
	IISc, Bangalore (Molecular Reproduction, Development and Genetics department), India	In glioma cells, β-catenin signaling pathway is regulated by Insulin-like growth factor binding protein-2 and it is a indicator of poor prognosis	Patil *et al.* (2016)
	Kashmir University (Dept of Biotechnology	Established the anti-neoplastic effect (C6 Glial Cells) of dasatinib and Caffeic Acid Phenethyl Ester	Balkhi *et al.* (2016)
	IIT Roorkee (Department of Mathematics)	Developed a mathematical model to elucidate brain tumor abrogation by immunotherapy with T11TS	Banerjee *et al.* (2015)
Lung cancer	Karunya University (Department of Biosciences and Technology), Coimbatore	Used 1, 2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and cholesterol lipo-ATRA to investigate its molecular therapeutic effect on lung cancer. The objective was to find whether it could enhance ATRA receptor, RAR-β expression in lung cells as it was lost in case of lung cancer	Berlin Grace *et al.* (2017)
	Saurashtra University (Department of Chemistry) with Institute of Biomedical Sciences, Taiwan	Evaluated a series of novel chemicals "bis (hydroxymethyl) indolizino (8,7-b) indole" hybrids against the growth of SCLC H526 cells in xenograft model. It was found that amongst all the hybrids, compound 17a was more effective when compared to etoposide and cisplatin and equipotent to irinotecan	Chang *et al.* (2017)
	Chittaranjan National Cancer Institute (Department of Immunoregulation and Immunodiagnostics)	Demonstrated the high expression of D2 receptors in non-small cell lung cancer (CD133 positive). They also established that D2 receptor activation was associated with inhibition of proliferation, which was associated with suppression of ERK1/2, AKT and down regulation of Oct-4 expression and MMP-9 (matrix metalloproteinase-9) secretion a cellular level	Roy *et al.* (2017)
	Sahyadri Science College (Kuvempu University)	Established the role of BP-1B in cancer associate angiogenesis	Thirusangu *et al.* (2017)
Cancer cervix	University of Kalyani (Department of Zoology)	Evaluated the effects of Conium maculatum on cervical cancer *in vitro* and established its ability to induce apoptosis	Mondal *et al.* (2014)
	ISF College of Pharmacy, Punjab	Developed and characterized cisplatin loaded nanofibers for therapy of cervical cancer	Agarwal *et al.* (2017)
	CSIR-Indian Institute of Chemical Technology (Natural Products Chemistry Division) Hyderabad	Evaluated the anticancer property of six novel compounds cancer cervix cell lines (ME-180 and HeLa)	Mallavadhani *et al.* (2014)

Hepato-cellular carcinoma	CSIR-Centre for Cellular and Molecular Biology, Hyderabad	Characterized major pathways regulating this atypical EMT through whole genome transcriptome profiling and molecular analysis, and identified a unique regulation of EMT by GSK-3β	Parveen *et al.* (2017)
	Loyola College (Department of Advanced Zoology and Biotechnology), Chennai	Evaluated antitumor Activity of Tetilladactyloidea (methanolic extract)	Krishnan *et al.* (2017)
	Nirma University (Institute of Pharmacy), Gujrat	Oryzanol was found to be effective	Panchal *et al.* (2017)
	Jamia Millia Islamia and AIIMS, New Delhi	Vanilin treatment inhibition of proliferation and decrease in mitochondrial production of ROS and reduction in mitochondrial membrance depolarization which resulted in enhanced apoptosis	Nah *et al.* (2017)
	Rajiv Gandhi Centre for Biotechnology (Kerala)	Solanumnigrum Unripe fruit fraction decreased resistance to Adriamycin which was associated with down-regulating multi-drug resistance protein (Mdr)-1	Jagadeeshan *et al.* (2017)
	Pondicherry University (Department of Biochemistry and Molecular Biology, Centre for Animal Research)	Troxerutin with copper generates oxidative stress in cancer cells: Its possible chemotherapeutic mechanism against hepatocellular carcinoma	Subastri *et al.* (2017)
	Sam Higginbottom Institute of Agriculture, Technology and Sciences (Allahabad)	Triterpenoids principle of Wedeliacalendulaceainhibited tumerous growth. They may be acting through the NF-κB pathway	Verma *et al.* (2017)
	Annamalai University	Chitosan nanoparticles protected Hepatocellular tissue against hepatocellular carcinoma induced by N-diethylnitrosoamine	Subhapradha *et al.* (2017)
	NMIMS University (Sunandan Divatia School of Science)	In insulin resistant liver cancer cell line (HepG2), Flavonoid content of Enicostemalittoraleblume enhanced glucose uptake by modulation of IRS-1/PI3K/Akt pathway	Mokashi *et al.* (2017)
	IPGMER, Kolkata	MiRNA199a-3p caused suppression of tumor growth, tumor invasion, migration and angiogenesis	Ghosh *et al.* (2017)
	Sam Higginbottom University of Agriculture, Technology &Sciences, Allahabad	Umbelliferon-α-d-glucopyranosyl-(2I'!1II)-α-Dglucopyranoside was effective in preventing DEN induced hepatic precancerous lesion development	Kumar *et al.* (2017)
	South Asian University, Chanakyapuri	Butyrate enhanced apoptiosis (mediated by ROS) and this occurred due to modulation of miR-22/SIRT-1 pathway	Pant *et al.* (2017)
	Birla Institute of Technology, Mesra, Ranchi	Found that some Schiff base analogues of 2-aminopyridine and 2-aminobezothiazole e.g. SSSC-33-((benzo[d]thiazol-2-ylimino) methyl)phenol) could effectively combat DEN induced hepato-cellular damage	Chacko *et al.* (2017)
	Yogi Vemana University, (Department of Biotechnology & Bioinformatics) Andhra Pradesh	4 key genes were identified (ADH1A, ADH1C, CXCR4 and ABCB1) which were found to be associated with cancer of liver	Gupta *et al.* (2017)
	Chittaranjan National Cancer Institute	In EAC bearing mice, selenium nanoparticles, when used in addition to cyclophaophamide, showed chemosensitizing and chemoprotective properties	Bhattacharya *et al.* (2017)
	Guru Nanak Dev University (Department of Botanical and Environmental Sciences) Amritsar	P. vittata showed high potential as a cancer chemopreventive agent	Kaur *et al.* (2017)
	Academy of Scientific and Innovative Research (AcSIR), New Delhi	Established the effect of PEGylated Betulinic acid (BA) in cancer therapy	Saneja *et al.* (2017)

inhibition of growth of tumor and potentiation of effects of other anticancer agents like 5-FU and oxaliplatin.

Shah *et al.* (2016) from institute of Pharmacy (Nirma University, Ahmedabad) evaluated the chemopreventive effect of *L. usitatissimum* extract in colon cancer (associated with type 2 diabetes). They established the usefulness of this extract as a chemoprevention agent and this effect was found to be mediated through CDK4 inhibition. Reddivari *et al.* (2016) from Yogi Vemana University (Andhra Pradesh) in collaboration with along with Pennsylvania State University evaluated the role of grape compounds on colon cancer stem cells. Grape compounds significantly suppressed colon cancer stem cells both in vitro and in vivo (rodent model) and this inhibitory effect was potentially mediated by Wnt/β-catenin signaling pathway.

Mitochondria plays an important role in cell bioenergetics and apoptosis. Impairment in the mitochondrial electron transport chain (ETC) is an important factor mediating uncontrolled proliferation in carcinogenesis. Researchers from Punjab University (Chandigarh) found that fish oil has dose dependent effect upon mitochondrial impairments and it augments apoptosis and thus decreases carcinogenesis (Agnihotri *et al.,* 2016).

Another group of researchers from Punjab University evaluated different ratios of corn oil and fish oil in experimental colon carcinogenesis and expression of different markers like Fas, Bax, Cyt-C and Bcl-2 expression. Treatment resulted in activation of intrinsic apoptotic pathway (as evidenced by increase in Cyt c release and Bax expression and decrease in Bcl-2 levels). (Sharma *et al.* 2016).

Leukaemia

Compounds with pyrazole moiety are important class of heterocyclic compounds. Department of Chemistry, Mysore University evaluated 1-aryl-3, 5-bis (het) aryl pyrazole derivatives against various cancer cell lines and found that 3-(1-(4-bromophenyl)-5-phenyl-1H-pyrazol-3-yl) pyridine (5d) had maximal anticancer activity particularly against leukemia and breast cancer cells (Ananda *et al.,* 2017).

Drug resistance is an important predictor of outcome of cancer chemotherapy. Researchers from Christian Medical College, Vellore (Hematology department) showed that protea some inhibitor bortezomib, when given in combination with arsenic trioxide for treatment of acute promyelocytic leukemia; the combination therapy successfully abolished the micro-environment-mediated resistance to arsenic trioxide (Ganesan *et al.,* 2016). Researchers from National Cancer Institute, Kolkata (Department of In Vitro Carcinogenesis and Cellular Chemotherapy)showed that Cu-5-SMAG is a promising anti-leukemia agent (predominant pro-apoptotic action), effect of which is not dependent upon phenotype of MDR. Cu-5-SMAG overcomes MDR in T-cell ALL by its inhibitory effect upon expression of EGFR/PI3K/Aktand by causing redox imbalance (Banerjee *et al.,* 2016). Another group from Department of Biochemistry and Medical Biotechnology (Stem Cell Research and Application Unit), Calcutta School of Tropical Medicine evaluated the mechanistic scenario of aberrations of p53 pathways (classical and hematopoiesis specific) in ENU (ethyl nitrosourea) model of leukemia (Chatterjee *et al.,* 2016). Das *et al.* (2016) established the regulatory role of estrogen receptor- alpha on casein kinase 2 alpha and its subsequent effect on enhancement of AKT activity and PML (tumor suppressor) degradation, resulting in increased cellular proliferation, migration and metastasis. Another group of researchers found that injectable chitosan-â-glycerophosphate gel amalgamated vincristine sulfate loaded dextran microspheres offered advantages like enhanced cytotoxicity on human leukemia cells (both in vitro and in-vivo) compared to the traditional formulation (Thakur *et al.,* 2016). In a mouse transplantable acute promyelocytic leukemia (APL) model, Patel *et al.* (2015) established the efficacy of immunotherapy (nonspecific DNA construct pVAX14) on survival when given in combination with ATRA (all-*trans* retinoic acid).

Brain Cancer

A group from Banaras Hindu University, Varanasi (Institute of Medical Sciences), demonstrated that transferrin receptor targeted Docetaxel loaded d-á-tocopherol polyethylene glycol 1000 succinate conjugated chitosan (TPGS-chitosan) nanoparticles had better cellular internalization, enhancement in relative bioavailability and cytotoxicity compared to their non-targeted counterpart (Agrawal *et al.,* 2017).

In *in-vitro* settings, Docetaxel (DTX) is very promising against glioma. However blood brain permeability limits its use. Shaw*et al.*,(2017) from Jadavpur University (Department of Pharmaceutical Technology) established that DTX-loaded nanoliposomes had better penetrability and thus it seems an important strategy to treat glioma with docetaxel. Bhattacharya *et al.* (2017) earlier demonstrated that in rodent glioma model, administration of sheep erythrocyte membrane glycopeptide T11-target structure is associated with apoptosis in glioma-associated brain endothelial cells and this effect is mediated via accumulation of p53 and associated inhibition of Raf/MEK/ERK and PI3K/Akt pathway which can provide critical insight to its mechanism of action.

16-hydroxy-cleroda-3,13-dien-16,15-olide (HCD), is a novel medicinal compound isolated from the plant "Polyalthialongifolia" has significant action on brain tumor cells. Bharathiar University (Department of Biotechnology, School of Biotechnology and Genetic Engineering) in collaboration with National Dong Hwa University, Taiwan evaluated the mechanism of action of HCD in brain tumor cell lines (glioma C6 and neuroblastoma N18 cell lines) and it was found that HCD induced autophagy was mediated via activation of ERK-1/2, p38 MAPK and ROS generation. (Thiyagarajan *et al.*, 2016). Arun *et al.* (2016) from University of Madras demonstrated that in glioma cell lines, Connexin 30 is an important modulator of IGF-1 receptor, which has actions like down-regulation of IGFR-1 and abolition of ErK etc. Connexin 30 additionally potentiated the effect of inhibitors of IGF-R. Patil *et al.* (2016) from IISc, Bangalore (Molecular Reproduction, Development and Genetics department), India found that in glioma cells, â-catenin signaling pathway is regulated by Insulin-like growth factor binding protein-2 and it is a indicator of poor prognosis. Balkhi *et al.* (2016) from Kashmir University (Department of Biotechnology) found established the anti-neoplastic effect (C6 Glial Cells) of dasatinib and Caffeic Acid Phenethyl Ester. Bhuvanalakshmi *et al.* (2015) established that the role of sFRP4 (secreted frizzled-related protein 4) which is a WNT agonist in epithelia-mesenchymal transition from their work using human glioblastoma cell lines U373 and U87. sFRP4 also acted as a chemosensitizer to temozolamide by reversing this transition. Banerjee *et al.* (2015) from IIT Roorkee (Department of Mathematics) developed a mathematical model to elucidate brain tumor abrogation by immunotherapy with T11TS.

Lung Cancer

All Trans Retinoic acid (ATRA) is an efficient drug for leukemia, but is not efficient therapy for solid cancers. Berlin Grace *et al.* (2017) from, Karunya University (Department of Biosciences and Technology), Coimbatore used 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and cholesterol lipo-ATRA to investigate its molecular therapeutic effect on lung cancer. The objective was to find whether it could enhance ATRA receptor, RAR-β expression in lung cells as it was lost in case of lung cancer. The study was done in experimental C57BL/6 mice model developed by inoculation of B16F10 and A549 human lung cancer cells.Both free and lipo-ATRA treatments showed an enhancement of RAR-β protein and gene expressions, indicating its induction on RAR β. However, the effect of lipo-ATRA was more compared to free ATRA treatment. Saurashtra University (Department of Chemistry), in collaboration with Institute of Biomedical Sciences, Taiwan evaluated a series of novel chemicals "bis(hydroxymethyl) indolizino (8,7-b) indole" hybrids against the growth of SCLC H526 cells in xenograft model. It was found that amongst all the hybrids, compound 17a was more effective when compared to etoposide and cisplatinand equipotent to irinotecan (Chang *et al.*, 2017). Roy *et al.* (2017) from Chittaranjan National Cancer Institute (Department of Immunoregulation and Immunodiagnostics) demonstrated the high expression of D2 receptors in non-small cell lung cancer (CD133 positive). They also established that D2 receptor activation was associated with inhibition of proliferation, which was associated with suppression of ERK1/2, AKT and down regulation of Oct-4 expression and MMP-9(matrix metalloproteinase-9) secretion a cellular level. Thirusangu *et al.* (2017), from Sahyadri Science College (Kuvempu University) established the role of BP-1B in cancer associate angiogenesis. Hudilkar *et al.* (2017) evaluated the chemo preventive effect of polyphenolic content of black tea and mechanism of this action in a model of lung cancer [benzo(a)pyrene and 4-(methylnitrosamino)-1-(3-pyridyl)-1- butanone-induced lung cancer] in A/J mice.

They found that the chemopreventive effect of polymeric black tea polyphenols (PBPs) was due to inhibition of inflammation and cellular proliferation and enhanced apoptosis and the molecular mechanisms included down-regulation of p38 and Akt phosphorylation.

Cancer Cervix

Mondal *et al*. (2014) from University of Kalyani (Department of Zoology) evaluated the effects of Conium maculatum on cervical cancer in vitro and established its ability to induce apoptosis. Prabhavathy *et al.* (2015) evaluated the effects of TNF-α on NF-βB expression in SiHa cells integrated with HPV16 E2. TNF-alpha sensitized NF-κB expression and the net effect resulted was increased senescence and survival. Mondal *et al*. 2015 established that in HPV 39 infected cervical cancer cell lines (ME-180 cell lines), artemisinin induced anti-proliferative and apoptosis inducing effect by repressing telomerase subunits and induction of apoptosis. Agarwal *et al.* 2017 from ISF College of Pharmacy, Punjab developed and characterized cisplatin loaded nanofibers for therapy of cervical cancer. Mallavadhani *et al.* (2014) from, CSIR-Indian Institute of Chemical Technology (Natural Products Chemistry Division) Hyderabad evaluated the anticancer property of six novel compounds in cancer cervix cell lines (ME-180 and HeLa).

Hepatocellular Cancer

Lot of good quality and important topics were addressed by researchers with regards to research in Hepatocellular cancer. Some of the research studies are shown in Table 1. Most studies used either cell line or chemical method to induce carcinogenesis. The studies ranged from characterization of novel compounds, plant extracts to elucidation of molecular pathway. Among all the cancers, hepatocellular cancer is one of the most explored areas among Indian researchers in preclinical research.

Status of Clinical Cancer Research in India

We collected data from CTRI, PubMed and clinicaltrials.gov top collect data on clinical research using different filters and keywords. Till now 1066 studies are registered in CTRI. The spectrum of studies comprised of randomized to non-randomized studies. Details are shown in Fig. 1. Among the completed studies, number of phase 3 studies (n=52) was highest, followed by phase 2 studies (n=37) compared to phase 1 studies. But the number was quite less when compared to data from USA. Number of multinational studies were also less (130 in India versus 2805 in USA), similar were result of meta-analysis and observational studies (data shown in Fig. 2).

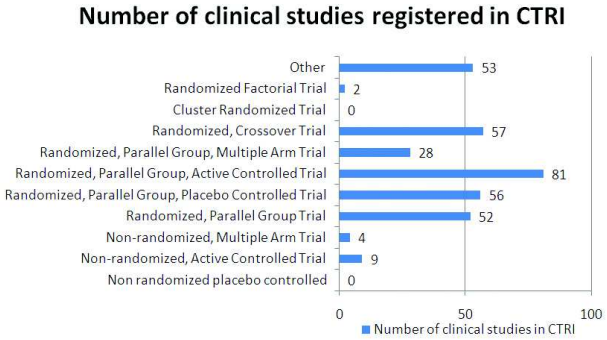

Fig. 1: Clinical studies registered in CTRI (design wise)

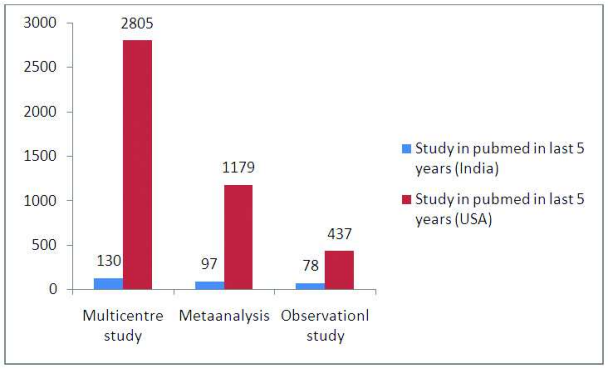

Fig. 2: Studies published in last 5 years (data obtained from PubMed)

So, to summarize, although India is progressing in terms of clinical research in cancer the pace is slow compared to developed country like USA. And some states of India are lagging behind. Government can take proper initiative in the same to improve the infrastructure and educational status of those states for further improvement.

Concluding Remarks

Many promising compounds are reported in preclinical research, but success rate in clinical trial is meager. DNA Ligase IV is responsible for sealing of double-strand breaks (DSBs) during nonhomologous end-

joining (NHEJ). SCR7 inhibits ligase IV in a dose dependent manner and which further activated intrinsic apoptotic pathways (Srivastava *et al.*, 2012). Later it was found that these agents were neither selective nor potent inhibitors of DNA ligase IV (Greco *et al.*, 2016). Compared to the amount of preclinical work, clinical translation is very less. This seems to be due to dissociation between preclinical and clinical research institutes or research departments. A good collaborative environment can improve cancer research status in India.

Reference

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