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1. How to write a Grant Proposal

Dr. Tanuja Teni
ACTREC, Tata Memorial Centre, Navi Mumbai-410210.

Academic success, in scientific research is largely dependent on the quality and quantity of grants received and research papers published. The grant proposal and the scientific manuscript are important tools in research with which, we obtain funds to conduct research and communicate our findings to the scientific community respectively. The process of writing a grant proposal and/or a manuscript can be a very challenging task particularly for the inexperienced researcher. However, these skills can be refined/taught and learned via scientific writing articles, books, courses and workshops. In the current era of information explosion, intense competition and reduced budgets by funding agencies, it is becoming increasingly important to be able to write a research proposal or a research paper of high quality. This article attempts to provide the readers few suggestions that may be useful in designing a winning grant application. The 'mantra', for success here is to deliver the combination of outstanding science with impeccable presentation.

Research grants are non-repayable funds provided by either government or private foundations and funding agencies to a recipient to conduct the proposed research after his/her grant application is reviewed and is successful. To get started you need to phrase your idea and plan the proposal, locate funding opportunities, determine funder's requirements and finally write your grant proposal.

❖ **Phrase your idea and plan the proposal**

A good grant begins with a great innovative research idea, which is based on a meaningful hypothesis. This further aids in the generation of the Research question(s). It is also essential to perform a thorough literature review to ensure that your research question is not been previously answered. The more realistic your idea is, the more possibility it will be funded. Procuring a grant is about convincing the reviewers that your idea is worthy and exciting. A bad idea cannot be disguised by good writing and neither a good idea, which is poorly presented can be successful. Clear and effective communication of your ideas combined with a high quality scientific approach in your written proposal will maximize your chances to obtain the desired funding (Table1). To make a lasting impression, your idea needs a well-crafted packaging.

Table 1: Shaping your Idea

- Hypothesis should be clear & testable
- Outcomes & Implications should be clear
- Identify questions that need to be addressed
- Design specific experiments that aid to test your hypothesis

It is also important to plan the project timeline and decide the team members with the required expertise. A clear and realistic proposed plan that is feasible to be completed within the grants time frame (usually range from 2 to 5 years) can boost a grant to the top of a reviewers list.

❖ **Locate funding opportunities**

Research grants are provided by a range of government or private organisations. They are called intramural funds if they are provided by your own institution and extramural if provided by other funding agencies. All funding agencies have information of their on-going funding schemes on their websites and it is important to find the suitable funding program. You can either submit the proposal to a government funding agency like Department of Biotechnology (DBT), Department of Science and Technology (DST). Indian Council of Medical Research (ICMR), and Council of Science and Industrial Research (CSIR) on your own initiative or respond to a call for proposal displayed on the agency's websites or apply to a suitable private funding agency like The Tata Trust, the Birla Trust etc. To increase the probability of funding, it is advisable to do extensive search of available grants and assess the type of projects financed by the different bodies. It is important to identify the source of funding that match your areas of research, expertise and capabilities. Most grants fund a specific project/equipment & require certain level of compliance and reporting. Grant applications unlike research paper submissions which have to be unique, allow you to work with templates & repurposed text.

❖ **Determine Funder's Requirements**

Before beginning an application, read and follow all instructions carefully and create a checklist of the funder's requirements. This is a frequently overlooked point. Studying successful proposals from colleagues, supervisors, institutional libraries or online databases will provide extremely useful guidance. Grants can be more speculative and self-promoting as compared to scientific manuscripts. You may generalise what your ideas may do for science and society in future, while a paper is more rigid and limited in terms of what you can speculate.

❖ **Preliminary Studies**

A preliminary study is generally a smaller scale version of the experiments, which provide the opportunity to test methods, equipment and other project aspects before its official beginning. Performing preliminary studies also allows researchers to identify and address possible shortcomings of the proposed project and help to identify any issues beforehand. Gathering preliminary data is crucial as it can serve as general proof of concept for your proposed project and also documents your credibility and research experience They also indicate your abilities to design studies and to analyse & interpret data. Your scientific publication record is a crucial assessment criteria in the context of your recent work and that possibly may be the area of

research in your submitted application. Hence, prior work relevant to the proposed project should be included and cited.

❖ **Writing your Proposal**

After locating a funding opportunity, planning your project and outlining your grant proposal, it's time to start writing your proposal. It is important to begin your grant writing early enough and schedule it to have a completed draft at least a month before the deadline. A good proposal is well prepared, thoughtfully planned and concisely packaged. Grant proposals generally contain the following elements tabulated in Table 2 below.

Table 2 : Proposal Elements

I.	Cover letter &Title
II.	Abstract & Keywords
III.	Research Plan
	Background and significance
	Preliminary results
	Specific aims
	Research design and methods
IV.	Budget
V.	Resources
VI.	Time line
VII.	Biosketches

The Elements of a proposal:

Within the word limit provided, describe your project as accurately, concisely and logically as possible and ensure inclusion of hypothesis, objectives, methods, research plan, significance & timeline. State why your proposal is unique, relevant & significant and why it needs to be supported.

➢ **Cover Letter and Project Title**

The cover letter with the grant proposal should be concise and professional, encompassing the submission details and enclosures. The title is the complete summary of the proposal and should open a bag in the reader's mind into which you drop your hypothesis and ideas. Use an appropriate, distinct and descriptive title for your project. Several people make the serious mistake of thinking that the title Is not very important. The Project title should be clever and should define the project clearly and accurately.

➢ **Keywords and Abstract**

The list of keywords is important for indexes and search engines and should not be an afterthought. The project abstract is the first element of the grant proposal and briefly describes every key element of the proposed project. It should encompass four key components. The problems/questions you are addressing, the hypothesis you are testing, the techniques you will be using and your overall work plan. Often reviewers are likely to make their opinion based on the abstract alone, which is the most important reason to write a succinct and complete abstract. It sets the first impression, as it is the first part that is read by the reviewer. The abstract should stand on its own and be understood even if separated from the rest of the application. Often applicants make the mistake of assuming that their hypothesis is true or do not summarise the full proposal. The abstract thus should be taken seriously & written last.

➢ **Background and Significance**

The purpose of this section is to evaluate & summarise the currently available relevant data in the literature and link your current project to the missing aspects of earlier research, leading to the rationale of the proposed research project. This section helps you to justify the study you are proposing. The important contribution or benefit to society by the findings of the study if any can help to convince, the reviewers & granting agencies of the worthiness of the project. For a basic study, critical evaluation of the existing studies and assessment of the missing aspect in the current project & how your project will result in an advancement of the field, should be emphasized.

A basic but thorough introduction to the subject is important and should not be skipped as it can help clarify the research project to reviewers of diverse backgrounds and require to be educated on the proposal by you. You need to guide them through your entire proposal slowly giving them the information they need to know. Emphasise, why you want to investigate these aims and why the research outcome is important and the significance of your work in the larger context.

➢ **Hypothesis, Specific aims and objectives**

This section focuses on the hypothesis of the study, the overall study aims and the specific objectives – primary and secondary objectives (for clinical studies).The hypothesis phrased should be in a manner that can be quantified and tested. The specific aims should clearly describe what research question the investigators are trying to answer by conducting the study. The problem being addressed should be clearly stated. Do not overreach, keep the project work reasonable, write clear and focused aims and methods. It is useful to have one or two objectives that are direct extensions of your preliminary data and one or two that are more innovative and imaginative. The relevance, significance and need/ impact of the current proposed research study should be stated.

➢ **Research design and methods**

Design experiments to test your hypothesis. Do not assume that your hypotheses are correct.

The choice of the study design has a significant implication on the magnitude of the funding required. It is important to choose a study design that is most likely to answer your research question, which is also feasible and provide the highest quality results. Ensure that the underlying science and planned experiments are sound, feasible to perform and complete. Show that your aims are realistic, give details how you can achieve all of them with the money you will receive and in the proposed grant time frame. Remember the reviewers could be from diverse fields and you need to guide them through every sentence and idea. If the study plans to use clinical samples then details of the samples size calculations, eligibility criteria, how outcomes will be measured etc. need to be detailed. Also an approval of the grant proposal by the Institute Ethics Committee (IEC) will be required.

It is not only important to include the experimental details of the study design but also the underlying logic of the proposed experiments. To make your research plan a winner address all questions your reviewers may have about your experiments. Additionally identify potential weaknesses in your protocols & research design and provide alternative techniques if your primary method fails. Your research plan should be adequately focused and include details on how you will perform the data collection, statistical analysis and interpretation of your data. If you propose to use novel techniques, explain why they are superior to existing ones. Constructing an outline of your research plan would be extremely beneficial. Use of diagrams can cut down on length and may aid to illustrate complex relationships that may not be clear through writing alone. If you are sloppy in your grant writing, reviewers are likely to question your abilities in the lab. Tips for the timely submission of your grant are tabulated below in the Table 3

Table 3: Suggestions to help your grant submission on time

- Schedule sufficient time for grant writing and revision and request multiple colleagues and mentors/experts to review your proposal.
- Make a spreadsheet with deadlines for you and your team, with accountability, and ensure writing for at least 30 minutes every day.
- Submit your application early to avoid last minute delays or technical problems with the online submission.

➢ **Budget, timeline and resources**

Create a reasonable budget with strong justification and define all assumptions and limitations. A budget that is unreasonably high or low will give the reviewers an impression that your project is over ambitious or lack focus. Remember to align your budget with funding agency's guidelines. Prepare and include a project timeline, which indicates your plan to work logically towards your project work. Also, include the time you and your team propose to spend on each portion of the project. It is also important to document the resources and assistance provided to you, by the home institution for running this study.

➢ **Biosketches**

This section includes the biodata of all the project members listed (usually 1-2 pages/person) which should highlight yours and your team's expertise and skills in the field. Convincing the reviewer of your expertise is important and choosing experienced team members is highly beneficial. This document includes the investigator's relevant credentials including their contact details, previous and current positions, training, funded projects and recent publications. This provides evidence of the applicant's qualifications, experience and expertise to successfully complete the proposed research and publish the results.

❖ **Style and Layout:**

A few simple tricks listed in Table 4 can boost the readability of your proposal. Write the proposal logically and clearly. In the limited space provided by the funding agencies, ensure that all central aspects of your project are exhaustively yet, briefly described. Formatting is important and inclusion of bold headings and white space make research proposals easier to read. Use bold only for subheadings and for important topic sentences. It would be beneficial to start each section with a summary of key points so that reviewers don't lose focus. Do not rely on unexplained jargon as reviewers may be from other research fields. Make sure to cite all relevant work unlike a research paper, the permitted citations in your grant may be limited to a certain number. In addition to listing references in your text, cite them correctly and in the style recommended by the funding agency protocol. To save editing time and errors, you can automate the formatting of your literature database. The two most widely used softwares are Endnote (Thomson Reuters) and Mendeley (Elsevier).

Make sure your proposal is grammatically correct as this helps reviewers to focus on the science and avoids chance of misunderstanding your goals and techniques. Also, avoid spelling errors and lengthy proposals that exceed word limits and avoid making an exhausting read for the reviewers. Use clear and simple language. A crisp and to the point write-up with technical details when necessary are appealing to the reviewers. A confident and transparent approach and clarity on what you want to do will take you on the path of success. Figures and tables serve as visual aids to understand your proposal and can be used to convey preliminary results, background and approach. Graphs, can be used to illustrate your long-term objective, your timelines, hypothesis and methods. Grant writing scheduling, should include time for rewrites and proofreads. Getting some science communication training and teaming up with collaborators can strenghthen your grant writing skills.Request other successful investigators or hired editing service providers to proofread your grant write up and provide feedback. The summarized guidelines listed in Table 4 may improve the readability of your proposal and the reviewer's interest.

Table 4: Guidelines to improve readability of your proposal

- Follow the three C's – Concise, Clear and Complete
- Make it visually appealing
- Make use of subheadings and a numbering system that ties it all together
- Avoid Jargon
- Cite all relevant work
- Include graphics and figures

Proposal Evaluation

Your proposal will be possibly, evaluated based on the following criterias listed in Table 5. The reviewer will check if your proposal fulfil the following requirements namely- Does your project have the potential to advance knowledge within the field and potential to benefit across other fields? Do the proposed research activities explore creative or original concept? Is the proposed plan logical, organized and based on the solid rationale? Are you well

qualified to conduct the proposed activities and are there adequate resources available to carry out the proposed activities?

Table 5: Evaluation criteria

- Intellectual merit
- Broader impacts
- Creativity
- Organization
- Expertise
- Resources

Successful grant applications and scientific papers share the following characteristics

- The write up is more positive, direct, energetic and concise
- Sentences are short key phrases and elements are highlighted
- The written matter is easy to understand and has fewer highly technical terms.
- Figures and tables are placed consciously.

Take rejections in your stride

The percentage of proposals funded by a funding agency may range from 14-30%, based on the available budget. Hence, majority of the proposals end up in rejection, which is difficult to take especially by early career researchers. Interestingly even successful researchers have probably had twice as many projects proposals rejected. The rejected grants provide a chance to learn how to find other opportunities, write better proposal and push past the rejection. Negative feedback can be one of the best learning experiences.

Conclusions:

Grants are important for academic success and writing a winning grant is a challenging task. Make your grant application a joy to read, rather a stimulating and easy reading experience for the reviewer. Develop your own simple and straightforward style and write your proposal with clarity, vigour, enthusiasm and in line with the funding agencies requirements. A crisp, formatted proposal with sufficient details, preliminary data and realistic plans will push your grant to the top of your reviewer list. An early start, proper scheduling which includes time for revision and proof reads will give the required boost. Creating a reasonable budget and defining all assumptions and limitations accompanied by a confident and transparent approach will steer the proposal onto the path of success. Making the proposal visually appealing, avoiding jargon and including figures will enhance your proposals value. Despite all efforts if your application is rejected don't be discouraged, treat it as a learning experience. Incorporate changes based on the reviewers' comments and submit the modified version to different funding agency.

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2. Mono-targeted vs multi-targeted agents for cancer therapy: Myth or reality

Subash Chandra Gupta[1,2*], Hitesh Singh Chaouhan[3], Anurag Sharma[4]
[1]Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi, 221005, India;
[2]Department of Biochemistry, All India Institute of Medical Sciences, Guwahati, India;
[3]Graduate Institute of Biomedical Sciences, China Medical University, 91 Hsueh Shih Road, Taichung 40402, Taiwan;
[4]Nitte (Deemed to Be University), Nitte University Centre for Science Education and Research (NUCSER), Division of Nanobiotechnology, Kotekar-Beeri Road, Deralakatte, Mangaluru, 575018, India
*Corresponding author
E-mail address: sgupta@bhu.ac.in

Cancer has been listed as the second biggest cause of death for the past several years. To our knowledge, the oldest description of cancer was reported in mummies in Egypt and dated back to about 3000 BC. However, the word cancer was not used during that period. The 'Cancer' word is coined from the Greek word 'karkinos', meaning 'carcinoma tumors'. The 'cancer' term was first used by Hippocrates (460–370 B.C.). To date, more than 100 cancer types have been reported in humans. Our understanding of cancer biology has significantly improved over the years. Spreading of the malignant cells to the surrounding organs (metastasis) accounts for 90% of cancer deaths. Yet, targeting primary tumor has been of high priority for researchers over the years. We now know that as many as 90% of certain cancer types are preventable. However, compared to developing prevention strategies, the major share of the cancer research fund is spent on its treatment.

It has been established that modulation of~ 500 signaling molecules associated with cell survival or cell death pathways are linked with tumorigenesis. However, the majority of the therapies target a single gene. The monotargeted drugs have been designed against molecular targets such as VEGF (avastin or bevacizumab), COX2 (celebrex), EGFR (erbitux), HER2 (herceptin), bcr-abl (gleevec), and TNF (enbrel, humira, remicade). After spending as much as $250,000, the present cancer treatment fails to promise better survival or quality of life. This is hard but true that the majority of cancer treatments are associated with failure than success. Moreover, due to the different genetic makeup, a successful drug does not have similar efficacy in patients belonging to a diverse population. For instance, gefitinib is an EGFR inhibitor used for lung cancer, giving a strong response only to one-tenth of the patients (1). However, it is an open question why only fewer (10%) of patients respond to the drug. Most often, even if a targeted drug is effective, how it is effective is unknown? In other words, the real target of the rationally designed drugs in patients is unknown. The increased levels of VEGF are associated with decreased survival of colon cancer patients. Avastin (Bevacizumab), designed against VEGF, is a monoclonal antibody. Avastin has been approved for treating colon and lung cancer (2, 3). Avastin does produce improvement in the median survival of metastatic colorectal cancer patients. However, the survival benefits are not always associated with the VEGF level (4). Similarly, survival of pancreatic cancer patients by Avastin was unrelated to plasma VEGF levels (5). How Avastin manifests its effect in patients is not very much clear. Herceptin (trastuzumab), a monoclonal antibody attaches to the extracellular domain of the human EGFR-2 (HER2/erbB-2) and makes the receptor unable to receive the growth signals. It is usually active in HER2-positive metastatic and resected breast cancer when given postoperatively (6). It has been observed that around 20% of women with breast cancer (HER2-positive) have responded positively to Herceptin. However, it is unclear why most HER2-positive women with breast cancer are insensitive to Herceptin (7). The resistance towards Herceptin has been observed in the patients within a year, the reason is again uncertain (8). In fact, the anti-tumor effect of Herceptin is associated with its antibody-dependent cellular toxicity, not through the downregulation of HER2 activity (9, 10). These examples indicate the complex mode of action of the target-specific cancer drugs. Understanding this complexity is an open challenge to oncologists.

If rationally designed target-specific drugs have little value on the survival of the patients, do we need to change the way the targets are approached? Could target-specific drugs fail because most tumors depend on multiple genes for their survival, growth, invasion, and metastasis? In contrast, most cancer drugs are designed against a single specific target (11). Is it possible that cancer cells are resistant to a mono-targeted drugs, but resistance is minimum if multiple targets are modulated (12, 13)? If so, the use of multi-targeted drugs or combinations of mono-targeted drugs will be more productive in treating cancer patients. In fact, a change in the paradigm has begun, and pharmaceutical companies are now focused on developing multi-targeted therapies. However, rationally designed multi-targeted drugs produce numerous side effects and are economically unsustainable to more than 80% of the human population (14, 15). For instance, one study showed that the combination of Erbitux with Avastin for colon cancer treatment made the therapy worse rather than better (16). In this regard, the use of dietary nutraceuticals as anti-cancer agents seems promising because of numerous reasons. First, nutraceuticals are generally considered safe so that they can be used for cancer prevention and therapy for both normal and cancer patients, respectively. Second, dietary agents are multi-targeted by nature as they target multiple signaling pathways. Third, in general, dietary agents are relatively inexpensive so that they can be afforded to every class of people worldwide. Fourth, dietary agents have been in use worldwide over the centuries, providing ''time-tested proof''. The scientific basis for the therapeutic value of these fascinating

molecules is already being proven in the 21st century.

During the last two decades, great emphasis has been given to the gene nutrient interactions to establish nutritional needs for preventing and treating chronic human diseases, including cancer. In the process, a concept of **"Nutrigenomics"** was introduced by Pelegrin in 2001 (17). Nutrigenomics refers to the interaction of nutrition with the genome. Nutrition-genome interaction can alter the digestion, absorption, and elimination of bioactive food components. The dietary components may arise from plants or animals and can alter the onset, incidence, progression, and/or severity of cancer. Some of the biologically active dietary components are capsaicin, celastrol, curcumin, epigallocatechin gallate (EGCG), genistein, quercetin, resveratrol, silibinin, and ɣ-tocotrienol. The dietary components can affect gene expression by acting on the human genome directly or indirectly. For instance, EGCG binds to TNF receptor-associated factor (TRAF) (18) and regulates tumorigenesis through the modulation of the NF-κB signaling pathway (19). The dietary components are reported to modulate multi-steps of tumor development, such as cell survival, proliferation, invasion, metastasis, and angiogenesis. The dietary components can modulate the genes associated with tumorigenesis. Some of the tumorigenesis genes modulated by dietary components include mitogen-activated protein kinase (MAPK), inflammatory molecules, NF-κB, Bcl-2, STAT-3, and Wnt/β-catenin. Curcumin and resveratrol are probably extensively studied dietary molecules. Resveratrol is reported to have a protective role against DNA damage. Especially, it can also promote apoptosis by regulating anti-and pro-apoptotic factors. Curcumin and resveratrol combination can reduce the expression of Fas, FasL, Bcl2, Bax, and Apaf1 (20).The combination of resveratrol and curcumin can also suppress kinases such as ERK1/2, p38, and JNK (20). Similar reports are available for other dietary agents as well. Several dietary agents have also been evaluated for their efficacy in human participants. For instance, over 244 clinical trials have documented resveratrol's efficacy, safety, and pharmacokinetics (21). The dietary agents have also been reported to modulate non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) (22).

At low doses, dietary agents are reported to enhance the efficacy of conventional therapies. For example, in combination with standard chemotherapies, EGCG was found to suppress sphere formation, a particular phenotype accountable for developing drug resistance caused by cancer stem cells (23). Resveratrol was found to enhance the efficacy of doxorubicin in a resistant hepatocellular carcinoma cell line (24, 25).

In conclusion, the beneficial effects of dietary agents have been reported by several lines of evidence. Nutrigenomics has helped in elucidating the multifaceted properties of dietary components. However, only a few agents have been tested by clinical trials. The discrepancies in the outcomes across the studies can not be ignored. Moreover, most conclusions on the efficacy of dietary agents are based on preclinical studies. We recommend more and more clinical trials involving a large number of populations before these fascinating molecules can be placed at the forefront of cancer therapeutics.

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3. Particulate Matter 2.5 as the pivotal player of lung carcinogenesis

Sukanya Ghosh, Paramita Ghosh, Dona Sinha
Dept. of Receptor Biology and Tumor Metastasis, Chittaranjan National cancer Institute,
37, S.P. Mukherjee Road, Kolkata-700026

Abstract
Air pollution is one of the major concerns related to human health as well as the environment. Air pollutants like particulate matter <2.5 μm in diameter (PM2.5) are the major contributors of morbidity and premature mortality owing to respiratory problems and cardiovascular problems. PM2.5 also cause neurotoxicity by triggering the progression of several psychological disorders and neurological diseases like Parkinson's disease and Alzheimer's disease. However, the most disastrous effect of PM2.5 lies in the fact that it may trigger the progression of lung carcinogenesis. In this review we have attempted to reflect a comprehensive account of the multiple mechanisms- inflammation, oxidative stress, DNA damage, immune response, genetic and epigenetic changes by which PM2.5 influences the process of lung carcinogenesis. We have further elucidated how this environmental challenge may be tackled and what future strategies may be undertaken to mitigate the hazardous effects of PM2.5.

Keywords
Air pollution, genetics and epigenetics, inflammation, lung cancer, oxidative stress, PM2.5.

1. Introduction

Air pollution is an environmental hazard which poses an impending threat to human health. Among the air pollutants, particulate matter (PM), ozone (O_3), nitrogen dioxide (NO_2) sulfur dioxide (SO_2) and carbon monoxide (CO), are the principal contributors of health-related issues including respiratory and cardio vascular ailments which in turn lead to morbidity and premature mortality. Among these PM especially PM2.5 and ultrafine particles pose an impending threat to human lungs by virtue of their deep penetration inside the lung alveoli. In this review we have not only to tried to represent the explicit statistics but have also encompassed a detailed account of the multiple mechanisms- inflammation, oxidative stress, DNA damage, immune response, genetic and epigenetic changes by which PM2.5 plays a significant role in the process of lung carcinogenesis. We have further envisaged the probable ways of confronting this environmental challenge and future strategies which may be implemented to mitigate the hazardous effects of PM2.5.

2. Estimates

Exposure to PM2.5 have both short- and long-term impact across all age groups of people, and especially children and elderly people are prone to maximum risk. The alarming concern lies over the fact PM2·5 exposure resulted in 4·2 million deaths and 103·1 million disability-adjusted life-years in 2015, and 59% of these effects were accounted from east and south Asia (Cohen et al., 2017). Previously PM exposure was associated with hospital admissions, mortality and morbidity, but lately scientific reports have deciphered that PM inflicted inflammation, lung cancer and genetic abnormalities (Carocci et al., 2015). According to the report of Global Burden of Disease Study PM2.5 is the fifth leading cause of global death. Moreover, with every 10μg/m^3 increase in PM2.5, there is 36% increase in chances of lung cancer (World Health Organization, 2016). The average life span of Europeans has decreased to about 3% due to these particles. The recommended annual average of PM2.5 by World Health Organization (WHO) is 10 μg/m^3 which has been recently revised to 5 μg/m^3 (World Health Organization, 2021). Whereas according to National Ambient Air Quality Standards, India the permissive annual average of PM2.5 is 12-15 μg/m^3 ("National Ambient Air Quality Standards (NAAQS) for PM | US EPA"). About 50% population living in 45% districts of India are exposed to hazardous annual mean PM2.5 concentrations much above the NAAQS level. In India, PM2.5 has caused about millions of deaths till 2015. In 2019, according to State of Global Air, PM2.5 caused 1.67 million deaths in India (Health Effects Institute and Institute for Health Metrics and Evaluation´s Global Burden of Desease project, 2020). In 2020, according to a Greenpeace Southeast Asia analysis of IQAir data, PM2.5 claimed almost 54000 lives in Delhi ("IQAir and Greenpeace report 2020 air pollution deaths – Air Quality Matters,").

3. Sources of PM

The major sources of PM which contribute to outdoor air pollution, include vehicular exhausts, refineries, power plants, factories, locomotives, ships, forest fires, volcanic eruptions as well as dust storms (Hricko, 2013). In developing countries the indoor source of PM primarily include burning of biomass fuel (wood, coal, cow dung, hay, straw, twigs etc.), mosquito coils (Khandelwal et al., 2019), incense sticks, frying of meat (McDonald et al., 2003) etc.

4. Why should we care?

PM2.5 has a diameter which is less than the size of a human hair. Owing to their small size, they remain longer in the atmosphere, increasing the risk of inhalation at a much higher rate. Though majority of the PM are trapped and cleared by mucociliary nasal process, PM2.5 are capable of entering deep within the lung alveoli. PM2.5 further evade the lung's respiratory barrier and enter into body's systemic circulation (Feng et al., 2016). Lately PM2.5 has been designated as a silent killer. These fine particles are associated with a large number of diseases ranging from asthma, chronic obstructive pulmonary disease (COPD) to lung cancer. PM2.5 is generated primarily due to anthropogenic activities and to control it we need to closely understand the hazards associated with it. The most interesting part lies in the fact that with reduction in PM2.5 levels almost 50% of air related health issues may be curbed.

5. PM2.5 induces lung cancer

Lung cancer due to PM2.5 is interlinked with genetic and epigenetic changes leading to inactivation of tumor suppressor genes (TSGs), overexpression of proto-oncogenes, alterations in cell cycle and chromosomal aberrations, generation of reactive oxygen species (ROS), DNA damage, evasion of autophagy and apoptosis (Santibáñez-Andrade et al., 2017). A type of non-small cell lung carcinoma (NSCLC)- lung adenocarcinoma is the most prevalent lung cancer type caused by PM2.5 exposure. Mutations in several genes such as TP53, epidermal growth factor receptor (EGFR), Kirsten Rat Sarcoma (KRAS) were prevalent in tumor tissues isolated from patients with NSCLC who were exposed to PM2.5. DNA damage due to bulky adduct (8-oxodG) formation (André et al., 2011), decrease in telomere length and mitochondrial dysfunction (Pieters et al., 2016) were some of the effects reported due to PM2.5 exposure on human alveolar macrophages (AMs). A report from different localities of Lucknow, India observed that PM2.5 increased the risk of lung cancers in humans due to polyaromatic hydrocarbons (PAHs) and metals such as Cr, Ni and Pb bound to it (Pandey et al., 2013). In China, it was observed that with increase in every 1 μg/m^3 of PM2.5 and 1 ng/mL of Zn, there was a 1.003-fold increase in lung cancer progression. PM2.5 even contributed to the malignant pleural effusion in lung cancer patients (Bai et al., 2021). PM2.5 may contribute to the abnormal cell proliferation, increase of cancer stem cells, epithelial mesenchymal transition(EMT), invasion, metastasis and increase in tumor growth (Li et al., 2019). In 2010, China witnessed a total of 91567 premature deaths due to lung cancer associated with PM2.5 exposure (Wang et al., 2019). In 2013, China recorded a total of 14000 lung cancer deaths due to PM2.5 in four major cities, the largest of which was observed at Shanghai (1565), and the smallest at Hefei (570) (Li et al., 2020). A 15%-17% mortality in lung cancer was observed due to PM2.5 exposure in 2016 in China(Li et al., 2018). A study from 295 Chinese counties, estimated that for every 10μg/m3 rise in PM2.5 there is 4.20% and 2.48% increase in risk of developing lung cancers among males and females respectively (Guo et al., 2020). PM2.5 related deaths was estimated to increase to 84102 by 2020 and to 244191 by 2030 (Wang et al., 2019). Although such an estimate was not conducted in India, yet the alarming increase in PM2.5 concentrations in the Indian environment is an inevitable peril for public health. If such a study could have been conducted in polluted Indian cities such as Delhi and Kolkata, the estimates might have resulted to similar numbers. Epidemiological studies denoting effect of PM2.5 on lung cancer have been tabulated below (Table 1).

Table 1: Epidemiological studies with PM2.5 exposure leading to lung carcinogenesis

Location	N	Dose of PM2.5 exposure and its associated components	Health effects	Results	Reference
Genk, Belgium	166	15 to 23 μg/m^3	Lung cancer	↓ telomere length 16.8% (95% CI: –26.0%, –7.4%, p = 0.0005) and 25.7% (95% CI: –35.2%, –16.2%, p < 0.0001) in mtDNA content mediated by SIRT 1 (19.5% and 22.5% respectively) for every 5μg/m3 increase in PM2.5.	(Pieters et al., 2016)
Lucknow, India	----	PM2.5 - 28.0–196.9 μg/m^3, Associated heavy metals; Pb- 33.9 ng/m^3, Ni- 38.5 ng/m^3, Cu- 29.4 ng/m^3, Cr- 8.4 ng/m^3, Cd- 1.17 ng/m^3, Fe- 54.3 ng/m^3	Lung carcinogenesis	ECR for Cr - 100.92 × 10^{-6}	(Pandey et al., 2013)
Taipei, Taiwan	61 (LC), 31 (CHF)	Ambient PM2.5 and its components (Zn, Al)	↑Malignant pleural effusion and ↑lung cancer risk	Malignant pleural effusion Adjusted OR = 1.517; 95% CI = 1.082–2.127 for PM2.5; Adjusted OR = 1.002, 95% CI = 1.000–1.005 for Zn Lung cancer risk (adjusted OR = 2.394, 95%CI = 1.446–3.964 for PM2.5; adjusted OR = 1.003, 95% CI = 1.000–1.005 for Zn for every 1 μg/m^3 of PM2.5 and 1 ng/mL of Zn respectively.	(Bai et al., 2021)
Yangtze river delta, China	---	Ambient PM2.5 (0-65 μg/m^3)	Mortality	14000 deaths, primarily due to lung cancer and lung damages.	(Li et al., 2020)
China	---	Ambient PM2.5 (2.56-84.52 μg/m^3); Mean: 43.02 μg/m^3	↑Lung cancer risk	↑ lung cancer risk by 4.20% (95% CI: 2.73%, 5.88%) and 2.48% (95% CI: 1.24%, 4.14%) with every 10 μg/m^3 rise in PM2.5 in males and females respectively	(Guo et al., 2020)
China	---	Annual average from 2020-2030 (predicted) (34.22-46.65 μg/m^3)	Mortality	Mortality due to lung cancer will rise from 84102 in 2020 to 244191 in 2030	(Wang et al., 2019).

Abbreviations: mtDNA- Mitochondrial DNA; SIRT - sirtunin; Pb- lead; Ni- nickel; Cu- copper; Cr- chromium; Cd- cadmium; Fe- iron; ECR-excess cancer risk; OR- odds ratio; CI- confidence interval; Zn- zinc; Al-aluminum

6. Progression towards lung cancer

PM2.5 is pleiotropic in nature and influences a multitude of signaling pathways which orchestrate the process of lung carcinogenesis. The varied oncogenic mechanisms (Fig.1) affected by PM.5 exposure have been described below:

6.1 Inflammation and immune response

Infiltration of artificial contaminants such as PM2.5 inside the lungs, caused secretion of cytokines and chemokines and inflammation (Arend et al., 2008). PM2.5 exposed lungs and alveolar air sacs were reported to be densely packed with leukocytes such as neutrophils, eosinophils and macrophages than that of normal lungs indicative of inflammation and allergic responses (Huang et al., 2008). Persistent inflammation has been often related with fibrosis and hyperplasia of the lung epithelium (Huang et al., 2008). An in vivo study suggested that PM2.5 exposure for 48h increased the number of alveolar macrophages (AMs) in the lungs (Jeong et al., 2019). It was established that the phagocytic rate as well as the phagocytic index of AMs were lowered with increase in PM2.5 concentration (Huang et al., 2008). AMs in response to PM2.5 expressed high levels of pro inflammatory cytokines associated with M1 macrophages such as interleukin-2 (IL-2), interferon-gamma (IFN-γ) and low levels of anti-inflammatory M2 cytokines such as IL-10, IL-4 and IL-13 in murine lungs (Park et al., 2011; Yoshizaki et al., 2010). PM2.5 also led to macrophage activation resulting in increased expression of vascular endothelial growth factor (VEGF) mRNA expression which was associated with angiogenesis. This in turn activated the CD47/ Sirpa signal regulatory protein α signaling pathway, which initiated tumor progression by affecting the phagocytosis of macrophages and inflammatory responses in the tumor microenvironment (Li et al., 2020). PM2.5 also induced inflammatory changes by upregulation of matrix metalloproteinase (MMP)-9, MMP-12, fibronectin, collagen and transforming growth factor-β (TGF-β) (Zhao et al., 2019). PM2.5 triggered asthmatic inflammation by upregulation of IL-5, IL-13, eotaxin and monocyte chemotactic protein-3 (MCP-3) by the toll like receptor-3/ TLR4 pathway in murine lungs (He et al., 2017). It even altered natural killer (NK) cell response in the lungs which made the lungs susceptible to severe lung infections (Zhao et al., 2014). PM2.5 activated secretion of IL-17 by pulmonary innate lymphoid cells which caused increased activity of chemokine (C-C motif) ligand 5 and lung damage (Jeong et al., 2019).

6.2 Oxidative stress, apoptosis and autophagy

PM2.5 may inflict a myriad of cellular events. Among them ROS-mediated DNA damage and cytotoxicity plays a major role in the progression of lung carcinogenesis. ROS upregulated mitogen-activated protein kinase(MAPK), extracellular regulated protein kinases, c-Jun, N-terminal kinase(JNK), p38 and downstream nuclear factor kappa light chain enhancer of activated B cells (NF- B) signaling pathways (Wang et al., 2017). High doses of PM2.5 also impaired AMs, leading them to destruction and apoptosis. Certain components of PM2.5 such as metals or organic components induced generation of ROS through cytochrome P4501A (CYP1A) and NADPH quinone oxidoreductase1 (Greenwell et al., 2002) which caused oxidative stress (El-Agamy et al., 2020). This led to increased ROS generation and deregulated lipid peroxidation, superoxide dismutase(SOD) and glutathione peroxidase(GPX) activity (Kouassi et al., 2010). Oxidative stress is associated with production of free radicals hydroxyl ions($OH\cdot$) and superoxide ions (O^{2-}) which inflicts oxidative DNA damage (Mehta et al., 2008) and induces cell death (Deng et al., 2014). ROS mediated over production of excessive Ca^{2+} ions, activated a series of inflammatory reactions, cell damage and induced apoptosis and necrosis in AMs (Brown et al., 2004). PM2.5 exposure also influenced upregulation of MnSOD, ROS generation along with considerable lactate dehydrogenase (LDH) production (Gurgueira et al., 2002). PM2.5 was further reported to cause apoptosis and autophagy in the lung epithelial cells via three pathways- the tumor necrosis factor- α (TNF-α) signaling pathway, the intrinsic caspase-8 pathway and the B cell lymphoma-2 (Bcl-2) pathway(Deng et al., 2014). ROS-mediated damages were observed with increased expression of autophagic genes such as Beclin-1 (Deng et al., 2017) and upregulation of CYP1A gene inducing cancer progression (Billet et al., 2008). PM2.5 maneuvered autophagy by inhibition of phosphatidylinositol 3-kinase (PI3K)/ protein kinase B(Akt)/mammalian target of rapamycin (mTOR) pathway owing to the exposure (Wu et al., 2020).

6.3 DNA damage, breaks and adduct formation

ROS is generally associated with DNA damage (Cho et al., 2018) lesions and epigenetic changes (Kim et al., 2017). PM2.5-induced oxidative stress has been associated with increased DNA damages (André et al., 2011; Oh et al., 2011)), chromosomal translocations (Rossner et al., 2014), formation of micronuclei (MN) and bulky DNA adducts (Eleonora Longhin et al., 2013). In both in vitro and in vivo models, certain components of PM2.5 such as organic nitro compounds [1-nitropyrene (1-NP), 1-nitrosopyrene(1-NOP)] led to DNA breaks and damages (Lemos et al., 2016) as well as significant increase in (acentric fragments) and MN formation in a dose dependent manner (Oh et al., 2011). PM2.5 increased the oxidation of certain bases and induced the formation of several propano, ethano and malonaldehyde exocyclic DNA adducts which were mutagenic in nature (Tubbs and Nussenzweig, 2017). On chronic exposure of PM2.5>70.2 μg the rate of production of DNA adducts increased (De Oliveira et al., 2018). PM2.5 exposure compromised the antioxidant activity of GPx and thioredoxin reductase which favored persistence of oxidative stress and formation of the DNA lesions (Forman et al., 2014). Some nano-particles present in PM2.5 were also able to penetrate the nuclear core of the lung cells and attack macromolecules as well as genomic DNA (Zou et al., 2017).

6.4 Genetic changes

Genetic changes associated with PM2.5 exposure have always been a matter of concern due to their impact on human health. In vitro studies revealed that both organic and inorganic components of PM2.5 resulted in the alteration of 17 genes of cell cycle, 12 of which were upregulated such as ectodysplasin A receptor (EDAR), fibroblast growth factor(FGF2), BCL2 related

protein A1(BCL2A1), complement component 6(C6), aryl hydrocarbon receptor (AhR) etc. and 5 were downregulated such as sirtuin1 (SIRT1), receptor tyrosine protein kinase (KIT) or CD117 (cluster of differentiation 117) , growth arrest and DNA damage-inducible41B etc. (Kim et al., 2018). Of these genes, EDAR and SIRT1 were associated with regulation of NF-κB (Kauppinen et al., 2013) and p53 (Han et al., 2008). CYP1A gene which regulates ROS production was also observed to be upregulated by PM2.5 (Kim et al., 2018). PM2.5 exposed lung tissues showed alterations of cell cycle and increased risk of carcinogenesis due to downregulation of p53 and upregulation of p21 (Zhao et al., 2017) and suppression of two other key TSGs namely $p16^{CDKNA}$ and anaphase promoting complex (APC) (Ding et al., 2016). On the other hand in vivo models suggested that PM2.5 influenced progression of lung carcinogenesis by robust expression of cell motility factor, MMP1 (Yang and Xiao, 2018), metastasis regulating molecule, "small" worm phenotype and Drosophila Mothers Against Decapentaplegic 1 (Yang et al., 2017), proto oncogenes FOS like 1, JUN (Gualtieri et al., 2012) and SRC proto-oncogene, non-receptor tyrosine kinase/ signal transducer and activator of transcription 3 (STAT 3) pathway which caused exhilaration of pro angiogenic factor, vascular endothelial growth factor A (Xu et al., 2016).

6.5 Epigenetic changes

Epigenetic alterations due to PM2.5 is another area of concern. An important TSG, p53 was downregulated in response to PM2.5 due to its promoter hypermethylation though ROS-Akt-DNA (cytosine-5-)-methyltransferase 3 beta (DNMT3B) (Zhou et al., 2016). This in turn bypassed apoptosis and aided uncontrolled proliferation and tumor progression. Other such effects of PM2.5 included hypermethylation of 15-lectin-type oxidized LDL receptor1 (15-LOX1/LOX2) gene which induced the overexpression of oncogenic cell functions (Li et al., 2019). Attenuation of promoter methylation of long interspersed nuclear elements (LINE) and iNOS genes, augmentation of promoter methylation of adenomatous polyposis coli (APC) and $p16^{CDKN2A}$ were observed in blood and lung tissues due to PM2.5 exposure (Ding et al., 2016). Short term exposure of PM2.5 triggered hypermethylation of Satellite α (Satα) repeats causing chromosome decondensation and degradation of blood plasma (Guo et al., 2014). Hypermethylation of 4 TSGs namely APC, p16, p53 and Ras Association Domain Family Member 1 (RASS1FA) along with decreased global methylation was reported in blood of healthy individuals exposed to PM2.5 which reduced the expression of these TSGs. (De Prins et al., 2013). PM2.5 regulates microRNAs(miRs) which are amongst the second most important contributing factor in the progression of lung cancer. miRs are involved in the upregulation and the downregulation of several genes contributing to tumor growth and metastasis. These genes may sometimes be TSGs as well as oncogenes in the lungs. Modulation of several miRs such as downregulation of miR802 was associated with increased expression of Rho Family GTPase 3 and bronchial dysplasia (Li et al., 2016). Downregulation of Let7A, miR15 and miR16 was associated with upregulation of two oncogenes such as c-Myc and KRAS promoting EMT (Wei et al., 2017) and downregulation of miR34a was linked with aggravation of Snail-1 mediated tumor growth and metastasis (Hong et al., 2015). PM2.5 reduced expression of miRNA182 and miRNA185 which activated several oncogenes such as Serpin B family members in human plasma (Liu et al., 2015). Similarly downregulation of miRNA144 was associated with increased Zinc Finger E-Box Binding Homeobox 1 expression which promoted EMT (Pan et al., 2015). Apart from miRNAs long noncoding RNAs (lncRNAs) are also influenced by PM2.5. Plasmacytoma variant translocation 1 (PVT1) was induced by PM2.5 to initiate the PVT1/miR-199a/caveolin1 signaling pathway operated lung cancer progression (Qi et al., 2021). Table 2 and Table 3 elucidates the direct and indirect impact of PM2.5 respectively on lung carcinogenic mechanisms in *in vivo* and *in vitro* models.

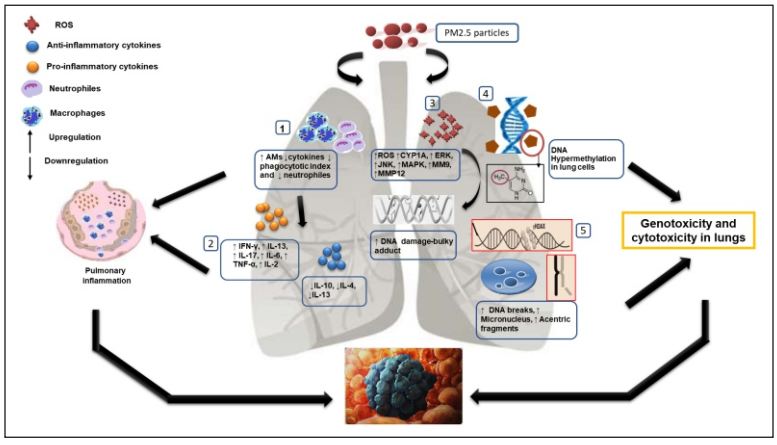

Fig 1: Pulmonary effects of PM2.5: PM2.5 exposure in the lungs (1) increases number of neutrophils and AMs with reduced phagocytic index promoting pulmonary inflammation, (2) upregulates pro-inflammatory cytokines like IL-2, IFN-ɣ, IL-13, IL-17, IL-13, IL-15, IL-6, TNF-α and downregulates anti-inflammatory cytokines like IL-10, IL-4, IL-13 promoting pulmonary inflammation. PM2.5 particles in lung cells (3) upregulates ROS production which causes DNA damage by formation of bulky adducts, (4) promotes DNA hypermethylation and (5) causes DNA breaks, and micronuclei. These events lead to genotoxicity, cytotoxicity of airway cells and pulmonary inflammation which together leads to lung carcinogenesis.

Table 2: Effect of PM2.5 on pathways directly associated with lung cancer

Model	Location of collection of PM2.5	Dose and duration of PM2.5 exposure	Effect	Mechanism	Reference
In vitro					
A549	USA	Long term exposure to 100 to 500 µg/mL	Dysregulation of actin cytoskeleton, metastatic activity	↓miR802, ↑RND3.	(Li et al., 2016)
	Shanghai, China	Acute exposure: 0, 5, 25, 50, 100, and 200 µg/mL of PM2.5 for 24h Chronic exposure: 0, 5, 50, and 100 µg/mL of PM2.5 for 24-48h	Tumorigenicity, EMT, metastasis, tumor recurrence, tumor growth and metastasis.	Chronic exposure: ↑ CD44, ↑ ABCG2, ↑ SOX2, ↑OCT4, ↓Let-7a, ↓miR-15, ↓miR-16, ↑ c-Myc, ↑KRAS, ↓miR-34a, ↑AXL, ↑ SNAIL-1.	(Wei et al., 2017)
	Dunkerque, France	6.33 µg/cm2-31.63 µg /cm^2 for 72h	Progression of cancer	↑CYP1A, ↑7-erf O-dealkylation, ↑EROD activity.	(Billet et al., 2008)
	Dunkerque, France	PM (LC10PM = 23.7 µg/ml), (LC50 =118.6 µg /ml) dPM (deadsorbed PM) dPM (deadsorbed PM) (Eq LC10 = 19.42 µg /ml), (Eq LC50 = 97.13 µg /ml) for 24h.	DNA damages in response to PM but not significant in response to dPM slowly leading to lung degradation and cancer	↑↑bulky adducts in the DNA (8-OHdG).	(André et al., 2011)
	Milan, Italy	10µg/cm^2 of summer PM and 10µg/cm^2 of winter PM for 24h each	EMT, tumors development, hypoxia, cell proliferation, differentiation, and transformation.	↑CYP1A1, ↑CYP1B1,↑ TIPARP in response to winter PM2.5, ↓ CDH1 promoting EMT, ↓ CPS1, ↓PTGER (promoter hypermethylation) in response to winter PM2.5 ↑GREM1 in response to both summer and winter PM2.5. ↑Fos gene (FOSL1), ↑JUN in response to summer PM2.5.	(Gualtieri et al., 2012)
A549 and H1299 (human non-small cell lung carcinoma cell)	Shenyang, China	50 µg/cm^2 for 72h	Enhanced mobility and cell proliferation	↑ EREG, ↑ IL-1A, ↑IL-1B, MMP1, ↑ MT1X and ↓TNFRSF1A, ↓ Tp53. ↑↑ MMP1.	(Yang et al., 2016)
A549 and H1975cells (Cellosaurus cell line)	Beijing, China	0 or 16 µg/cm^2 for 48h	Autophagy, EMT and metastasis	↑lncRNA loc146880 ↑lc3b, ↑beclin1, ↓E-cadherin, ↑vimentin	(Deng et al., 2017)
A549 and H292(pulmonary lymph node metastasis cells) cells	Shenyang, China	(0, 5, 10, or 20) µg/cm^2 for 72h	EMT, metastasis and drug resistance.	↑Smad1, ↓Smad6, ↓Smad7, ↑Vimentin, ↓E-cadherin.	(Yang et al., 2017)
BEAS-2B cells	Wuhan, China	100 µg/mL for 24h	Chronic airway inflammation and vascular remodeling.	↑STAT 3 pathway, ↑VEGFA	(Xu et al., 2016)
	Wuhan, China	120µg/m^3 for 10 days	Hypermethylated promoter regions of p53, loss of repair and apoptosis.	↓ 1 DNMT1, ↑DNMT3B, ↓p53, ↑ Akt, ↑ DNMT3B, ↓p53	(Zhou et al., 2016)
	Zhanjiang, China	100 µg/mL for 24h	Autophagy	↓PI3K/Akt/ mTOR pathway.	(Wu et al., 2020; Liu et al., 2015)

Model	Location of collection of PM2.5	Dose and duration of PM2.5 exposure	Effect	Mechanism	Reference
	Milan, Italy	7.5 μg/cm^2 for (1-40) h	Single- and double stand breaks, cell cycle perturbation	↑8-oxodG adducts after 24h, ↑ γH2AX levels after 3h, ↑phosphorylation of ChK2, no changes in p53 phosphorylation after 24h, ↑frequency of double nuclei and MN after 40h	(Longhin et al., 2013)
16-HBE14o cells	Paris	10 μg/cm^2 for 18h	Angiogenesis and airway inflammation.	↑ EGFR, ↑IL-1, ↑ chemokine gene GRO-α, ↑ AREG	(Baulig et al., 2007)
	Paris and Beijing, China	25 μg/cm^2 for 24h	Angiogenesis, airways inflammation, tumor growth and metastasis.	↑ IL-6, IL-8, TNF-α and GM-CSF.	(Baulig et al., 2007; Zhou et al., 2015)
16HBE cells, NCI-H292, BEAS-2B and NHBE (primary normal bronchial epithelial cells).	Paris	50 μg/cm^2 for 24h	Apoptosis. DNA damage, genomic instability, cancer progression.	↑ AhR, ↑ BCL2, ↓E2F1-	(Ferecatu et al., 2010)
NCI-H23	Kowloon Tong, Hong Kong	5 μg/ml for 28 days	Oncogenic cell overexpression	↓15-LOX1/LOX2 gene (Hypermethylation).	(Li et al., 2019)
H292	Shenyang, China	10 and 20 μg/mL for 24h, 48h and 72h	Cell cycle perturbation and risk of carcinogenesis	↑p53, ↑CDK2 after 24h of exposure, ↑ Cdc2, ↑cyclin B after 48h of exposure ↓↓p53, ↑p21 after 72h of exposure.	(Zhao et al., 2017)
HEL12469 (Human embryonic lung fibroblast)	Prague and Ostrava	B(α)P extracted from PM2.5 (25 μM) for 24h	DNA breaks and translocation events in chromosome 7 and lung carcinogenesis	↑ γH2AX levels.↑ γH2AX levels.	(Rossner et al., 2014)
Human AM/L132	Dunkerque City, France	18.84, 37.68, 56.52, 75.36, and 150.72 μg/mL	Perturbed cell cycle, apoptosis, lung carcinogenesis	Alteration in TP53-RB gene signaling pathways, ↑p21 ↓CCND1 gene, hyperphosphorylated RB	(Abbas et al., 2016)
In vivo studies					
C57BL/6 mice serum	USA	100 to 500 μg/mL for 28 days.	Bronchial dysplasia.	↑RND3	(Li et al., 2016)
Bet1A cells implanted in mice	Kowloon Tong, Hong Kong	5 μg/ml for 28 days	Lung tumors appeared	↓15-LOX1/LOX2 (Hypermethylation)	(Li et al., 2019)
NC/Nga mice	China	1, 10, and 100 μg/mouse	Lung damage and increased probability of carcinogenesis	↑eosinophils and neutrophils, ↑TNF- ,↑IL-4 and ↑IL-10	(Zhang et al., 2015)
Balb/c mice	Wuhan, China	10, 31.6, or 100 μg/mouse	Airway Inflammation	↑IL-13 and ↑IL-4, ↑TSLP, ↑(Th)1/Th2 cytokine	(Liu et al., 2017)
Wister rat (blood, lung tissues)	Zhejiang, China	0.088 to 0.102 per 1 μg/m^3 increase in the pollutant concentration for 4h, 7 days, 14 days, or 28 days in spring and autumn	Loss of cell cycle control, invasion and metastasis and inflammation.	↓p16^{CDKN2A}, ↓APC (Hypermethylation) ↑LINE1 and↑ iNOS (Hypomethylation)	(Ding et al., 2016)
Lung tissues of Wister rats	Shenyang, China	0.4 mg/mL/rat once every 15 days and sacrificed after 15 days of the exposure	Alterations of cell cycle and increased e risk of carcinogenesis	↑p53, ↑CDK2 after 24h of exposure. ↑ (Cdc2), ↑cyclin B after 48h of ↓↓p53, ↑p21 after 72h of exposure.	(Zhao et al., 2017)

Abbreviations: 8-OHdG - 8-oxo-7,8-dihydro-2' –deoxyguanosine; ABCG2: ATP-binding cassette super-family G member 2; AhR - Aryl hydrocarbon receptor; AREG – Amphiregulin; Cdc2 - cell division cycle protein 2; CDH1 - Cadherin-1; CPS1 - carbamoyl-phosphate synthase 1; DNMT - DNA (cytosine-5)-methyltransferase; EREG – Epiregulin; EROD - ethoxyresorufin-O-dealkylase activity; FSH – follicle stimulating hormone; GREM1 - gremlin 1; iNOS - inducible nitric oxide synthase ; LH – luetenizing hormone ; lncRNA – long non-coding RNA; MMP – matrix metalloproteinase; OCT4 - octamer-binding transcription factor 4; RND3 - resistance-nodulation-division 3; SOX2 - SRY (sex determining region Y)-box 2; STAT 3 - signal transducer and activator of transcription 3; TIPARP - TCDD Inducible Poly (ADP-Ribose Polymerase; TNFRSF1A - tumor necrosis factor receptor superfamily 1A; TP53- tumor protein 53; VEGFA - vascular endothelial growth factor.

Table 3: Influence of PM2.5 on pathways indirectly associated towards the progression of lung cancer

Model	Location of collection of PM2.5 sample	Dose and period of exposure of PM2.5	Health effects	Mechanism	Reference
In vitro studies					
HBECs	Shanghai, China	100, 300 and 500μg/cm^3 for 24 h	Lung inflammation	↑IL-1β, ↑IL-6, ↑IL-8, ↑MMP- 9 and ↑ COX-2. ↑MAPK and NF-κB pathway	(Wang et al., 2017)
	Wuhan, China	25 μg/ml to 200 μg/ml for 24 h	Lung inflammation	↑IL-6, ↑IL-8, ↑MMP9, ↑MMP12, ↑ fibronectin, ↑collagen and ↑TGF-β	(Zhao et al., 2019)
A549/THP -1	Milan Torre Sarca, Italy	10 μg/cm^2	Oxidative stress, DNA damage	↑IL-6, ↑IL-8 and ↑IL-1β, ↑ γH2AX	(Longhin et al., 2013)
A549	District of Abidjan (Côte d'Ivoire)	3, 6, 12, 24 or 48 μg/cm^2 for 72 h	Oxidative stress in the lungs	Alteration of lipid peroxidation, SOD and GPX activity.	(Kouassi et al., 2010)
	Seoul. Korea	W-PM2.5 (78.51μg/ml-426.91μg/ml) O-PM2.5 (937.24 μg/ml-1962.80μg/ml)	Inflammatory response, cell death, DNA damage, and apoptosis.	Alteration of 17 genes related to cell cycle ↑C6, ↑AhR, ↑EDAR, ↑FGF2, ↑BCL2A1 etc ↓SIRT1, ↓KIT, ↓GADD45B etc.	(Kim et al., 2018)
	Beijing, China	8, 16, 32, or 64 μg/cm^2 for 6, 12, 24 or 48 h	Apoptosis and autophagy	↑TNF-α induced pathway, ↑ intrinsic apoptotic pathway (↑ Bax, ↓BCL-2), and ↑LC3, ↑Beclin-1.	(Deng et al., 2014)
	Shanghai, China	25, 50, 100, and 200 μg/mL for 24 h	Cell membrane disturbance, decreased cellular viability, increased intracellular oxidants, cellular injuries and DNA damage	↑↑LDH for every 50μg/ml increase in PM2.5 concentration.	(Zou et al., 2017)
	Gaithersburg , Maryland	100μg/ml for 24 h	Spontaneous and UV-induced mutagenesis	↑Bulky DNA adducts ↓Nucleotide Excision Repair	(Mehta et al., 2008)
BEAS-2B	Suwon City, Korea	35.37 g/m^3 for 24 h for a period of 1 month	DNA breakage and damage (oxidized purines and pyrimidines)	↑ CYP1A, ↑EROD ROS formation such as such as O-, H2O2, and OH-, ↑MN	(Oh et al., 2011)
	Cache Valley in northern Utah/south eastern Idaho	0.69 μg/ml,1.37, 2.72, or 4.03 μg/ml	Pulmonary fibrosis	↑IL-1R, ↑IL-6R, ↑pSTAT3	(Watterson et al., 2007)
16HBE-14o		50 μM/cm^2 for 0.5 h,1h,2h and 3h	Inflammation of the airway and oxidative stress	↑IL-25, ↑IL-33, ↑MDA, ↑ NF-κB pathway, ↑IL-8 and TNF, ↑IL-4, ↑IL5, ↑endothelin-1	(Bao et al., 2017)
Chinese hamster lung cell line (V79 cells)	Triunfo, Brazil	6.50-8.50 μg/m^3 PM2.5 (10 and/or 20 mg/mL, for 3 h)	↑genotoxic damage and carcinogenesis.	↑↑micronucleus due to organic compounds such as Benzo(α)pyrene.	(Lemos et al., 2016)

In vivo studies					
C57BL/6 mice	Zhengzhou in China	2.5, 5, and 10 mg/kg/mouse	Smooth muscle cell proliferation, contraction of bronchi, bronchial hyper-reactivity	↑p38 and JNK pathways ↑ETA mRNA, ↑ p38, ↑MEK1/2 pathways,↑ETB.	(Yan et al., 2015)
	Wuhan, China	110 μg/m^3 for 48 weeks	Respiratory illness, emphysematous lesions and airway inflammation	↓Lung function, ↑MMP9, ↑MMP12, ↑fibronectin, ↑collagen, ↑TGF-β1	(Zhao et al., 2019)
	St. Louis, MO, USA	25μl of 200μg PM2.5 containing solution for 24h and 48h	Pulmonary inflammation	↑ frequency of AMs and neutrophils, IL-17, ↑CCL-5.	(Jeong et al., 2019)
C57BL/6 and Balb/c mice	Shanghai, China	20μL of 20mg/mL SRM1649b (urban dust)	Autoimmunity and airway diseases	↑PAH, ↑Th-17, ↑IL-17A, ↑IL-22, ↑IL-23R	(Van Voorhis et al., 2013)
C57 mice	Shanghai, China	100 μg/day/mouse for two days	Oxidative stress and lung inflammation	↑Pro-inflammatory cytokines, ↑ IL-1β, ↑IL-6, ↑IL-8 and ↑MMP-9	(Wang et al., 2017)
Wister rats	In a place near the Steel Plant of Taiyuan, Shanxi Province, China	1mg/kg, 5mg/kg, 10mg/kg for 72h	Inflammation of lungs	↓ AM phagocytosis and ↑NK cells, ↑TNF- and ↑IL-6 in lungs	(Zhao et al., 2014)
	Beijing, China	0.3 mg, 0.75 mg, 2 mg, 5 mg	Loss of lung elasticity deposition of black particles, inflammation, pulmonary fibrosis and tumors.	↑AM, ↑ phagocytes in alveolar wall, ↑TNF-α, ↑IL-6	(Huang et al., 2008)
	Shanxi Province, China	1, 5, or 10-mg/kg body weight for 72h	Respiratory illness and lung infections.	Impaired NK cells, AMs activity	(Zhao et al., 2014)
	Chepstow, UK	200 μg/ml for 4h	Pulmonary inflammation, epithelial hyperplasia and fibrosis.	↑ Cytosolic calcium, ↑NF- B and ↑AP-1, ↑TNF-α production.	(Brown et al., 2004)
	Beijing, China	0.3 mg, 0.75 mg, 2 mg, 5 mg of PM2.5 per 0.5 mL salin for 58 days	Inflammation, epithelial hyperplasia and pulmonary fibrosis.	↓AMs, ↓phagocytic activity	(Huang et al., 2008)
	Zhejiang, China	Ambient PM2.5 levels of TRAP for 4hs, 7 days, 14 days and 28 days.	Genomic instability, cell cycle perturbation, invasion and metastasis in lungs.	↑Methylation in the promoter regions of LINE-1 ↓$p16^{CDKN2A}$ and ↓APC	(Ding et al., 2016)
Sprague-Dawley rats	Taipei city	24 h/day, 7 days/week, for 16 weeks	Blood vessel damage, cardiovascular disease, hyperglycemia	↑IL-6, ↑fibrinogen, ↑myocarditis, ↑HOMA-IR, ↑HbA1c, ↑thickness of aortic walls	(Yan et al., 2014)
	Massachusetts, USA	100-500μg/m^3 for 1-5h	Lung tissue damage and oxidative stress.	↑Water content in tissues, ↑serum LDH levels, ↑MnSOD	(Gurgueira et al., 2002)
		CAPs from Ambient PM2.5 (9.2 ± 6.2 μg/m^3) and 10 minutes concentrated PM2.5 (164.5 ± 213.2 μg/m^3) for 5h/day for 10 days	↑ respiratory frequency, lower flows, and lower volumes, shallow breathing pattern. Inflammatory responses in blood.	↑TNF-α, ↑CRP, ↑WBC, ↑hematocrit, ↑Hb, and ↑absolute lymphocytes and ↑monocytes in blood	(Clougherty et al., 2010)
Balb/c mice	Wuhan Tianhong, China	10, 31.6, or 100 μg/mouse	Airway Inflammation	↑IL-13 and ↑IL-4, ↑TSLP, ↑(Th)1/Th2 cytokine	(Liu et al., 2017)
	Shenyang, China	Ambient PM2.5 for 2 weeks	Peribronchiolar allergic inflammation	↑Frequency of neutrophils, goblet cells, eosinophils, ↑IL-13, ↑IL-15, ↑eotaxin and ↑MCP-3, by the TLR-2/TLR-4/MyD88 pathway.	(He et al., 2017)
NC/Nga mice	Okayama, Japan	200 μg of precipitate in 25 μl of sterile phosphate buffer (PB)	Airway Inflammation	↑IL-1β, ↑eosinophil, ↑epithelial NLRP3, ↑ LPS ↑ IFN-ɣ , ↑Th1 and Th2 cytokines.	(Ogino et al., 2014)

ICR mice	Seoul, Korea	100µl of 10mg/kg per mice for 28 days	Oxidative stress and inflammation	↑IL-1, ↑TNF-α, and ↑IL-6, ↑Th0-type cytokine (IL-2), and ↑Th1-type cytokines (IL-12 and IFN-γ), ↑HSP 1a, ↑HSP 8, and ↑SOD, ↑MMP-15, ↑MMP-19.	(Park et al., 2011)
Four week old male AJ mice	Sao Paulo, Brazil	0.864 µg/day (56.16 µg after 65 days) for 5 days/week, 3 months	Alterations in anti-oxidant system, cell cycle perturbations, induction of apoptosis, cell differentiation and promotion of oncogenic signaling.	↑ 8-oxo-dG, ↑ εdAdo and ↑ **1,N2-εdGuo**, ↑Global levels of 5-hmC	(De Oliveira et al., 2018)

Abbreviations: **1,N2-εdGuo** - 1-N2-etheno-2'-deoxyguanosine; 8-oxo-dG - 8-Oxo-2'-deoxyguanosine; BAT - brown adipose tissue; ET1 - endothelin-1; *GFAP* - Glial fibrillary acidic protein; H2O2- hydrogen peroxide; LDL- low density lipoprotein; NH2OH – hydroxylamine; Nrf2 - nuclear factor erythroid 2–related factor 2; PBMC - *Peripheral Blood Mononuclear Cells*; ROCK - Rho Associated Coiled-Coil Containing Protein Kinase 1; SREBP1 - Sterol regulatory element-binding transcription factor 1; TIMP - tissue inhibitor of metalloproteinases; WAT - white adipose tissue; WT – wild type; εdAdo - 1,N 6-Etheno-2′-deoxyadenosine *"Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less."- Marie Curie*

7. Future perspectives

Air pollution is a real threat to the health and well-being of mankind. India is ranked thirteenth among the most polluted countries in the world and Delhi is ranked first among the list of the most polluted cities of the world whose annual average is 153 ug/m^3 (IQAir, 2019). PMs are the most dreadful amongst these air pollutants as many of their adsorbed constituents are pro carcinogenic in nature. High levels of PM2.5 (>60ug/m^3) is associated with DNA damage, mutation in bases and lung carcinogenesis. An individual is never exposed to any particular pollutant but to a mixture of pollutants, thus effective mitigation strategies might be formulated accordingly (Laumbach et al., 2015). About 80% of the outdoor pollution is associated with vehicular exhausts, which are the major source of PAHs in PM2.5. Therefore, replacement of the fuels such as petrol and diesels with compressed natural gas (CNG) and liquefied nitrogen gas (LNG) might be very effective. In Iran this fuel shift was effective to mitigate outdoor pollution (Ghorani-Azam et al., 2016). Production of superior quality motor engines like Japan and other western countries which are characterized with minimal fuel consumption may also solve the problem (Che et al., 2011). Public transportation systems should be more upgraded so that people are able to avail them in a much easier way thereby generating dual benefits of economic travel and greener environment (Rizwan et al., 2013). Spike in the fuel price has also proved to be effective to lower pollution levels (Barnett and Knibbs, 2014). Industries may be imposed with penalties for not adhering to the environmental standards. However, environmental standards should be established by continuous monitoring of the air quality, the pollutants present in the environment and the origin of the pollutants. The Indian government has already taken important measures to control air pollution which includes usage of unleaded petrol, reduction of sulphur and benzene content in diesel and promotion of CNG as fuel. In January 2016, Delhi government took a major step to curb air pollution levels, by permitting road travel of odd and even number plated private vehicles only on odd and even days respectively. This brought down pollution to a huge level in Delhi (Sharma et al., 2016). National Air Quality Monitoring Programme monitors the pollutant level nation-wide. Spending 8 to 10h in a clean and healthy environment is necessary to reduce the adverse effects due to such pollutants (Rizwan et al., 2013). Communication and collaboration between different groups of science such as toxicology, environmental health, chemistry, organics and physics may help solve the problem in a much effective way. Government measures alone will not solve the problem. Awareness among the people is of utmost importance along with certain measures taken by the government to control the levels of the pollutants. Public awareness is also mandatory through campaigns. If common mass is not involved in solving the problem, human health will remain at stake (Ghorani-Azam et al., 2016). Certain precautionary measures should be taken by people who are exposed to these pollutants in outdoor and indoor environments. A qualified mask should be used, especially by people having respiratory or any cardiovascular diseases while stepping out of the house. During smog remaining indoors is the best possible measure with closed doors and windows. Mosquito repellents are a major source of indoor PM2.5 and hence mosquito nets are the most effective solution (Xing et al., 2016). As we have seen that oxidative stress is the major response occurring due to pollutant exposure, food rich in antioxidants such as omega-3 fatty acids in fish oil, herbs, minerals, essential amino acids, other detoxifying or protective agents, and fibers should be consumed. Majority of plant food contain vitamin E, C and A which act as ROS scavengers and also have anti-inflammatory and antiviral activities shows better result.

The COVID-19 pandemic locked people inside their homes in 2020 and cities saw clear skies with lower PM2.5 levels in the atmosphere. This can be attributed to the fact that the roads had lesser or no vehicles and industries were halted owing to the spread of infection. Lesser emissions curbed air pollution to a huge level all over the world. News reported that the Himalayas (Dhauladhar mountain range of Himachal) was viewed from Jalandhar, Punjab, India which is almost 200kms away for the first time in 30 years due to a huge down gradation of pollution levels during this pandemic (" Hindustan Times,"). However as soon as people were back to their normal lives, the pollution level again surged up. Perpetual rise of air pollutants will not only

worsen conditions of those who are already suffering from respiratory and cardiovascular diseases but also of the population as a whole. Thus, we need to understand the importance of the situation and take small steps towards curbing air pollution. We along with the help of the government may create an environment which may be safe for breathing clean air.

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6th session of the UN General Assembly: 14th September 2021-27th September 2021, New York City, US

47th G7 Leaders' Summit 2021: 11th June - 13th June 2021, Carbis Bay, St Ives, Cornwall (UK)

4. Abstract/Report for World Cancer Research Day celebration at RGCB

Rajiv Gandhi Centre for Biotechnology (RGCB), Thiruvananthapuram, joined hands with Indian Association for Cancer Research (IACR) to celebrate World Cancer Research Day (WCRD) on 24th September 2021 in raising awareness and commitment to cancer research.

The purpose is to support cancer research towards significant discoveries that can make a positive difference in the quality of patients' lives. The primary aim of the WCRD campaign is to promote initiatives focused on bringing resources and attention to cancer research, demonstrating the value of cancer research to public health, and inviting people to be part of this global movement. The conference encouraged collaborative research to address the current challenges facing us and the opportunities to accelerate results in cancer research for a future without cancer.

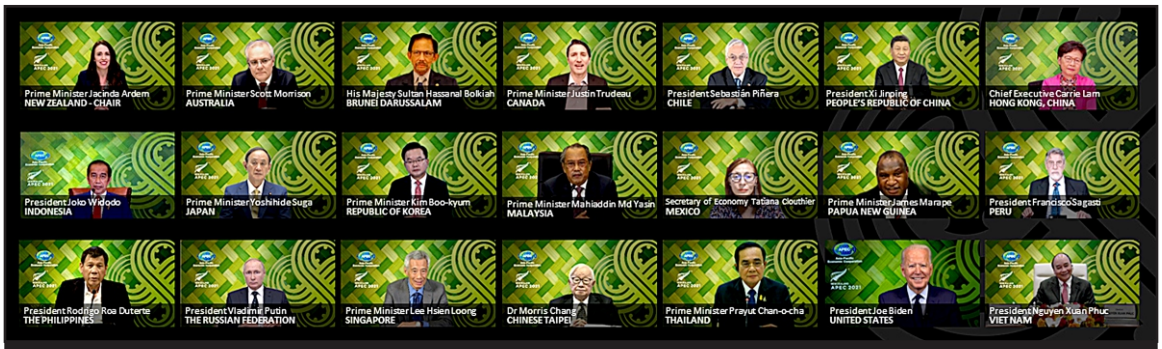
The conference was in webinar format where Professor Chandrabhas Narayana, Director, RGCB, introduced all four speakers who are prominent cancer researchers in India in his introductory talk.

1. Professor Bhudev C Das, Chairman of Amity Institute of Molecular Medicine and Stem Cell Research, talked about the priorities in current cancer research with emphasis on cancer relapse, chemoresistance, and tumor heterogeneity. He also indicated a roadmap towards personalized cancer therapy to overcome these challenges.
2. Following him, Professor Sharmila Bapat, Scientist G from National Centre for Cell Science, Pune, dived deeper into an intriguing yet challenging world of tumor heterogeneity. She described how clinical diversity and tumor microenvironment contribute towards inter-tumor heterogeneity.
3. Next, Dr. Aman Sharma, Founder Director of ExoCan Healthcare Technology Pvt. Ltd., a scientist who turned his research into a successful business model with the support of the Biotechnology Industry Research Assistance Council (BIRAC), New Delhi, advocated exosome as a non-invasive potential tool for cancer diagnostics and therapeutics.
4. In the final talk, Professor Bushra Ateeq from IIT, Kanpur, a Wellcome Trust Fellow, and Shanti Swaroop Bhatnagar awardee, gave her insight on the importance of prostate cancer research. She explained how androgen signaling plays a critical role in prostate cancer progression and therapeutic outcomes.

At the closer, Dr. Priya Srinivas, a senior scientist at RGCB and Secretary of IACR, delivered the vote of thanks.


41st Annual Conference of Indian Association for Cancer Research
"Combating Cancer : Biology to Therapy to Drug Resistance"
&
An International Symposium on: Cancer & Stem Cells
theme of the conference
"Cancer Doesn't Care! We Care!"
75th Year of Indian Independence : आजादी का अमृत महोत्सव
Greetings !
2nd – 5th March 2022
Organized by
Amity Institute of Molecular Medicine & Stem Cell Research (AIMMSCR)
Amity University Uttar Pradesh, NOIDA, India
IACR-2022
Cancer has become the leading cause of death in humans surpassing cardiovascular, metabolic and other diseases. Despite huge advancements in diagnosis and treatment of cancer, the five-year survival rate is still very low around the globe. Moreover, resistance to chemotherapeutic drugs/radiation therapy often leading to cancer recurrence and relapse is the major global challenge that the whole world is facing. Therefore, there is an urgent need for rigorous research and innovation in the field of cancer biology to develop modern tools for early detection, identify relapse-free therapeutic approaches and also to provide platforms for discussing latest findings and path-breaking advances and spreading global awareness to combat cancer. Considering huge challenges in the war against cancer, we are organizing 41st IACR annual conference (IACR-2022) on "Combating Cancer: Biology to Therapy to Drug Resistance" along with an international symposium on "Stem Cell and Cancer".
Theme of the Conference is "Cancer Doesn't Care, We Care!".
AMITY UNIVERSITY, NOIDA
Important Dates
Abstract submission starts on:
20th September 2021
Abstract submission ends on:
15th January 2022
Registration commence from:
1st November 2021
Details of Registration are now available at conference website
https://amity.edu/iacr2022
Email: iacr2022@amity.edu
Mob : 8882295071
Organizing Secretary
Prof. (Dr.) Bhudev C Das
Chairman & H. G. Khorana Chair Professor, Amity Institute of Molecular Medicine & Stem Cell Research (AIMMSCR), DEAN, Health & Allied Sciences, Vice President, Amity Science, Technology & Innovation Foundation (ASTIF), Amity University Uttar Pradesh
Tel: +(91)-0120- 4586855
Mob: 9810566870, 9810537835
Venue
Amity Institute of Molecular Medicine & Stem Cell Research, J-3 Block, Amity University, Sector 125, Noida, Uttar Pradesh 201313

MET Gala: 13th September 2021, The Metropolitan Museum of Art, NY, USA,



Asia-Pacific Economic Cooperation (APEC) 2021: 16th July, 2021, New Zealand

Black Lives Matter Rally 2021: London, Cape Town, Sydney, Tokyo, Paris, USA


INDIAN ASSOCIATION FOR CANCER RESEARCH
1980