b. **List of ten best papers of the candidate, highlighting the important discoveries not to be exceed 3000words).**

1. Majumder, R.; Banerjee, S.; Paul, S.; Mondal, S.; Mandal, M.; Ghosh, P.; Maity, D.; Anoop, A.; Singh, N. D. P.; **Mandal, M.*** *Riboflavin-Induced DNA Damage and Anticancer Activity in Breast Cancer Cells under Visible Light: A TD-DFT and In Vitro Study*. **J. Chem. Inf. Model.** 2024, 64 (14), 5580–5589. https://doi.org/10.1021/ACS.JCIM.4C01104. **IF: 5.6**

Targeted treatments for breast cancer that minimize harm to healthy cells are highly sought after. Our study explores the potentiality of riboflavin as a targeted anticancer compound that can be activated by light irradiation. Here, we integrated time-dependent density functional theory (TD-DFT) calculations and an in vitro study under visible light. The TD-DFT calculations revealed that the electronic charge transferred from the DNA base to riboflavin, with the most significant excitation peak occurring within the visible light range. Guided by these insights, an in vitro study was conducted on the breast cancer cell lines MCF-7 and MDA-MB-231. The results revealed substantial growth inhibition in these cell lines when exposed to riboflavin under visible light, with no such impact observed in the absence of light exposure. Interestingly, riboflavin exhibited no/minimal growth-inhibitory effects on the normal cell line L929, irrespective of light conditions. Moreover, through EtBr displacement (DNA-EtBr) and the TUNEL assay, it has been illustrated that, upon exposure to visible light, riboflavin can intercalate within DNA and induce DNA damage. In conclusion, under visible light conditions, riboflavin emerges as a promising candidate with a selective and effective potent anticancer agent against breast cancer while exerting a minimal influence on regular cellular activity.

2. Majumder, R.; Banerjee, S.; Mandal, M.; Patra, S.; Das, S.; **Mandal, M.*** *A Virtual Drug Discovery Screening Illuminates Campesterol as a Potent Estrogen Receptor Alpha Inhibitor in Breast Cancer*. **J. Med. Chem.** 2024, 67 (12), 10321–10335. https://doi.org/10.1021/acs.jmedchem.4c00766. **IF: 6.8**

Breast cancer remains a global health challenge, and innovative strategies are required to target estrogen receptor α (ERα), a key player in its development. This study investigates the potential of campesterol, a natural phytosterol, as an ERα inhibitor for breast cancer. Our approach integrates in silico, in vitro, and ex vivo experiments to assess the therapeutic potential of campesterol. In silico analyses highlight campesterol as a promising ERα ligand with favorable binding affinities and dynamic properties. Structural analysis reveals conformational changes in ERα upon campesterol binding. In vitro studies confirm the selective growth inhibition of campesterol against ERα-positive breast cancer cells. This study extends to ER+ breast cancer patient-derived organoids (PDOs), showing the effectiveness of campesterol in ERα-positive breast cancer PDOs. Importantly, it emphasizes the receptor-specific nature of campesterol, providing insights into its context-dependent action. In conclusion, campesterol displays potential as an ERα inhibitor, offering new avenues for ER+ breast cancer treatment.

3. Banerjee, S.; Majumder, R.; Mukherjee, B.; **Mandal, M.*** *Selective ADA2 Inhibition for Enhancing Anti-Tumor Immune Response in Glioma: Insights from Computational Screening of Flavonoid Compounds.* **Int. J. Biol. Macromol**. 2023, 253 (Pt 7). https://doi.org/10.1016/J.IJBIOMAC.2023.127453. **IF: 8.2**

Brain tumors, particularly gliomas, remain difficult to treat due to their complex and dynamic microenvironment and high mortality rate. The presence of tumor-associated macrophages (TAMs) is considered one of the primary factors contributing to a poor prognosis in Glioma. Previous reports have linked elevated levels of Adenosine deaminase 2 (ADA2) with immunosuppression, tumor progression, and angiogenesis via MAPK, PDGFβ signaling pathway in the glioma microenvironment. In contrast, Adenosine deaminase 1 (ADA1), another type of adenosine deaminase, plays a pivotal role in purine metabolism, which is essential for lymphocyte survival. Hence, selectively targeting ADA2 while preserving ADA1 activity could offer a viable approach for regulating macrophage polarization and enhancing the anti-tumor immune response. In pursuit of this objective, our study employed a computational approach, unveiling the remarkable attributes of Daidzin, characterized by its exceptional specificity, and binding affinity towards ADA2 while displaying minimal affinity towards ADA1. Furthermore, Define Secondary Structure of Proteins (DSSP) analysis revealed that Daidzin elicits conspicuous conformational alterations within the dimerization domain of the ADA2 receptor, which could have a crucial impact on its activity. However, the ADA1 structure remained unaltered. Our study offers the potential use of Daidzin as a specific therapeutic agent for modulating the tumor microenvironment and revolutionizing glioma management.

4. Biswas, A.; Rajesh, Y.; Das, S.; Banerjee, I.; Kapoor, N.; Mitra, P.; **Mandal, M.*** *Therapeutic Targeting of RBPJ, an Upstream Regulator of ETV6 Gene, Abrogates ETV6-NTRK3 Fusion Gene Transformations in Glioblastoma*. **Cancer Lett. 2022**, 544, 215811. https://doi.org/10.1016/J.CANLET.2022.215811. **IF: 9.75**

Fusion genes are abnormal genes resulting from chromosomal translocation, insertion, deletion, inversion, etc. ETV6, a rather promiscuous partner forms fusions with several other genes, most commonly, the NTRK3 gene. This fusion leads to the formation of a constitutively activated tyrosine kinase which activates the Ras-Raf-MEK and PI3K/AKT/MAPK pathways, leading the cells through cycles of uncontrolled division and ultimately resulting in cancer. Targeted therapies against this ETV6-NTRK3 fusion protein are much needed. Therefore, to find a targeted approach, a transcription factor RBPJ regulating the ETV6 gene was established and since the ETV6-NTRK3 fusion gene is downstream of the ETV6 promoter/enhancer, this fusion protein is also regulated. The regulation of the ETV6 gene via RBPJ was validated by ChIP analysis in human glioblastoma (GBM) cell lines and patient tissue samples. This study was further followed by the identification of an inhibitor, Furamidine, against transcription factor RBPJ. It was found to be binding with the DNA binding domain of RBPJ with antitumorigenic properties and minimal organ toxicity. Hence, a new target RBPJ, regulating the production of ETV6 and ETV6-NTRK3 fusion protein was found along with a potent RBPJ inhibitor Furamidine.

5. Kundu, M.; Das, S.; Nandi, S.; Dhara, D.; **Mandal, M.*** *Magnolol and Temozolomide Exhibit a Synergistic Anti-Glioma Activity through MGMT Inhibition*. **Biochim. Biophys. acta. Mol. basis Dis**. 2023, 1869 (7). https://doi.org/10.1016/J.BBADIS.2023.166782. **IF: 6.63**

Temozolomide (TMZ) is the leading chemotherapeutic agent used for glioma therapy due to its good oral absorption and blood-brain barrier permeability. However, its anti-glioma efficacy may be limited due to its adverse effects and resistance development. O6-Methylguanine-DNA-methyltransferase (MGMT), an enzyme associated with TMZ resistance, is activated via the NF-κB pathway, which is found to be upregulated in glioma. TMZ also upregulates NF-κB signaling like many other alkylating agents. Magnolol (MGN), a natural anti-cancer agent, has been reported to inhibit NF-κB signaling in multiple myeloma, cholangiocarcinoma, and hepatocellular carcinoma. MGN has already shown promising results in anti-glioma therapy. However, the synergistic action of TMZ and MGN has not been explored. Therefore, we investigated the effect of TMZ and MGN treatment in glioma and observed their synergistic pro-apoptotic action in both in vitro and in vivo glioma models. To explore the mechanism of this synergistic action, we found that MGN inhibits MGMT enzyme both in vitro and in vivo glioma. Next, we established the link between NF-κB signaling and MGN-induced MGMT inhibition in glioma. MGN inhibits the phosphorylation of p65, a subunit of NF-κB, and its nuclear translocation to block NF-κB pathway activation in glioma. MGN-induced NF-κB inhibition results in the transcriptional inhibition of MGMT in glioma. TMZ and MGN combinatorial treatment also impedes p65 nuclear translocation to inhibit MGMT in glioma. We observed a similar effect of TMZ and MGN treatment in the rodent glioma model. Thus, we concluded that MGN potentiates TMZ-induced apoptosis in glioma by inhibiting NF-κB pathway-mediated MGMT activation.

6. Rajesh Y, Biswas A, Kumar U, Banerjee I, Das S, Maji S, Das SK, Emdad L, Cavenee WK, **Mandal M***, Fisher PB. *Lumefantrine, an antimalarial drug, reverses radiation and temozolomide resistance in glioblastoma.* **Proc Natl Acad Sci** U S A. 2020 Jun 2;117(22):12324-12331. **IF- 9.4.**

Glioblastoma multiforme (GBM) is an aggressive cancer without currently effective therapies. Radiation and temozolomide (radio/TMZ) resistance are major contributors to cancer recurrence and failed GBM therapy. Heat shock proteins (HSPs), through regulation of extracellular matrix (ECM) remodeling and epithelial mesenchymal transition (EMT), provide mechanistic pathways contributing to the development of GBM and radio/TMZ-resistant GBM. The Friend leukemia integration 1 (Fli-1) signaling network has been implicated in oncogenesis in GBM, making it an appealing target for advancing novel therapeutics. Fli-1 is linked to oncogenic transformation with up-regulation in radio/TMZ-resistant GBM, transcriptionally regulating HSPB1. This link led us to search for targeted molecules that inhibit Fli-1. Expression screening for Fli-1 inhibitors identified lumefantrine, an antimalarial drug, as a probable Fli-1 inhibitor. Docking and isothermal calorimetry titration confirmed interaction between lumefantrine and Fli-1. Lumefantrine promoted growth suppression and apoptosis in vitro in parental and radio/TMZ-resistant GBM and inhibited tumor growth without toxicity in vivo in U87MG GBM and radio/TMZ-resistant GBM orthotopic tumor models. These data reveal that lumefantrine, an

FDA-approved drug, represents a potential GBM therapeutic that functions through inhibition of the Fli-1/HSPB1/EMT/ECM remodeling protein networks.

7. Parekh A, Das S, Parida S, Das C, Dutta D, Mallick S, Dr. Wu HP, Kumar BNP, Bharti R, Dey G, Banerjee K, Rajput S, Bharadwaj D, Pal I, Dey KK, Rajesh Y, Jena B, Biswas A, Banik P, Pradhan AK, Das S, Das A, Dhara S, Fisher PB, Dr. Wirtz D, Mills G, **Mandal M*.** Multi-nucleated cells use ROS to induce breast cancer chemo-resistance in vitro and in vivo. **Oncogene**, 2018. May 10. doi: 10.1038/s41388-018-0272-6. **IF- 8.459**

Although there is a strong correlation between multinucleated cells (MNCs) and cancer chemo-resistance in variety of cancers, our understanding of how multinucleated cells modulate the tumor micro-environment is limited. We captured multinucleated cells from triple-negative chemo-resistant breast cancers cells in a time frame, where they do not proliferate but rather significantly regulate their micro-environment. We show that oxidatively stressed MNCs induce chemo-resistance in vitro and in vivo by secreting VEGF and MIF. These factors act through the RAS/MAPK pathway to induce chemo-resistance by upregulating anti-apoptotic proteins. In MNCs, elevated reactive oxygen species (ROS) stabilizes HIF-1α contributing to increase production of VEGF and MIF. Together the data indicate, that the ROS-HIF-1α signaling axis is very crucial in regulation of chemo-resistance by MNCs. Targeting ROS-HIF-1α in future may help to abrogate drug resistance in breast cancer.

8. Bharati R, Dey G, Banerjee I, Dey KK, Parida S, PrasanthKumar BN, Das CK, Pal I, Mukherjee M, Mishra M, Pradhan AK, Emdad L, Das SK, Fisher PB. and **Mandal M*.** *Somatostatin receptor targeted liposome with diacerin inhibit IL-6 for breast cancer therapy*, **Cancer Letters** 2016 Dec 24;388:292-302, **IF- 7.36**

Selective targeting to the tumor niche remains a major challenge in successful cancer therapy. Somatostatin receptor 2 (SSTR2) is overexpressed in breast cancer cells thus making this receptor an attractive target for selective guidance of ligand-conjugated drug liposomes to the tumor site. In this study, a synthetic somatostatin analogue (SST) was used as SSTR2 targeting agent and Diacerein was employed as therapeutic molecule. Diacerein loaded liposomes (DNL) were prepared and they were further decorated with the synthetic and stable analogue of somatostatin (SST-DNL). Fabricated liposomes were nano-size in range and biocompatible. SST-DNL displayed significantly better anti-tumor efficacy as compared to free Diacerein (DN) and DNL in breast cancer models. Enhanced apoptosis in breast cancer cells was detected in SST-DNL treated groups as monitored by cell cycle analysis and changes in expression level of apoptotic/anti-apoptotic proteins Bcl-2, Bax, cleaved Caspase 3 and PARP. SST-DNL more effectively inhibited the oncogenic IL-6/IL-6R/STAT3/MAPK/Akt signalling pathways as compared to DN or DNL in cancer cells. In addition, SST-DNL effectively suppressed angiogenesis and cancer cell invasion. In vivo tumor growth in a MDA-MB-231 mouse xenograft model was significantly suppressed following SST-DNL treatment. In xenograft model, immunohistochemistry of Ki-67 and CD-31 indicated that SST-DNL improved the anti-proliferative and anti-angiogenic impacts of Diacerein. In vivo pharmacokinetic studies in rats showed enhanced circulation time in the DNL or SST-DNL treated groups as compared to free

DN. Considering all of these findings, we conclude that SST-DNL provides a novel strategy with better efficacy for breast cancer therapy.

9. Bharati R, Dey G,Ojha P, Rajput S, Jaganathan S, Sen R and **Mandal M***(2015). *Diacerein mediated inhibition of IL-6/IL-6R signaling induces apoptotic effects on breast cancer.* **Oncogene**, 28;35(30):3965-75. **IF- 8.459**, Citation- 3

Interleukin-6 (IL-6) signaling network has been implicated in oncogenic transformations making it attractive target for the discovery of novel cancer therapeutics. In this study, potent antiproliferative and apoptotic effect of diacerein were observed against breast cancer. In vitro apoptosis was induced by this drug in breast cancer cells as verified by increased sub-G1 population, LIVE/DEAD assay, cell cytotoxicity and presence of terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)-positive cells, as well as downregulation of antiapoptotic proteins Bcl-2 and Bcl-xL and upregulation of apoptotic protein Bax. In addition, apoptosis induction was found to be caspase dependent. Further molecular investigations indicated that diacerein instigated apoptosis was associated with inhibition of IL-6/IL-6R autocrine signaling axis. Suppression of STAT3, MAPK and Akt pathways were also observed as a consequence of diacerein-mediated upstream inhibition of IL-6/IL-6R. Fluorescence study and western blot analysis revealed cytosolic accumulation of STAT3 in diacerein-treated cells. The docking study showed diacerein/IL-6R interaction that was further validated by competitive binding assay and isothermal titration calorimetry. Most interestingly, it was found that diacerein considerably suppressed tumor growth in MDA-MB-231 xenograft model. The in vivo antitumor effect was correlated with decreased proliferation (Ki-67), increased apoptosis (TUNEL) and inhibition of IL-6/IL-6R-mediated STAT3, MAPK and Akt pathway in tumor remnants. Taken together, diacerein offered a novel blueprint for cancer therapy by hampering IL-6/IL-6R/STAT3/MAPK/Akt network.

10. Venkatesan P, Puvvada N, Dash R, Kumar BNP, Sarkar D, Azab B, Pathak A, Kundu SC, Fisher PB, **Mandal M*.** (2011) *The potential of celecoxib-loaded hydroxyapatite-chitosan nanocomposite for the treatment of colon cancer*. **Biomaterials** 32(15): 3794-3806**. IF- 10.317**

Celecoxib has shown potential anticancer activity against most carcinomas, especially in patients with familial adenomatous polyposis and precancerous disease of the colon. However, serious side effects of celecoxib restrict its generalized use for cancer therapy. In order to resolve these issues and develop an alternative strategy/preliminary approach, chitosan modified hydroxyapatite nanocarriers-mediated celecoxib delivery represents a viable strategy. We characterized the nanoparticle for morphology, particle size, zeta potential, crystalinity, functional group analysis, entrapment efficiency, drug release and hemocompatibility. The effects of celecoxib-loaded nanoparticles on colon cancer cell proliferation, morphology, cytoskeleton, cellular uptake and apoptosis were analysed in vitro. Further, we evaluated the antiproliferative, apoptotic and tumor inhibitory efficacy of celecoxib-loaded nanocarriers in a nude mouse human xenograft model. Nanoparticles exhibited small, narrow hydrodynamic size distributions, hemocompatibility, high entrapment efficiencies and sustained release profiles. In vitro studies showed significant antiproliferation, apoptosis and time-dependent cytoplasmic

uptake of celecoxib-loaded Hap-Cht nanoparticles in HCT 15 and HT 29 colon cancer cells. Additional in vivo studies demonstrated significantly greater inhibition of tumor growth following treatment with this modified nanoparticle system. The present study indicates a promising, effective and safe means of using celecoxib, and potentially other therapeutic agents for colon cancer therapy.