Laboratory of Epigenetics and Diseases

AREAS OF INTEREST

Drug discovery and development has undergone a paradigm shift with increasing stress on 'lead optimization' in the preclinical stage in order to reduce the attrition rate in the later stages of drug development. Biomarkers of drug efficacy and toxicity are becoming a key need in the drug development process. Genomic and proteomic techniques are involved in predicting the toxicity of new chemical entities and also in identifying new drug targets. Mass spectral-based proteomic technologies are ideally suited for the discovery of protein biomarkers in the absence of any prior knowledge of quantitative changes in protein levels. Proteomics also facilitate the development of strategies for the therapeutic interventions and clinical management of cancer through the identification of protein molecules involved in metastasis. Nanotechnology is one of the very frontiers of science today. It refers to the projected ability to construct items from the bottom up, using techniques and tools being developed today to make complete, high performance products. It also offers enhanced benefits of specific targeting of drugs such as enhancing the efficacy of pharmaceutical cargoes encapsuled within nano-formulations. Future of drug discovery lies in appropriate utilization of these states-of-art techniques. Thus, my endeavor is to utilize genomic and proteomic techniques in discovering new drug targets as well as identifying disease specific proteomic and genomic markers. *Furthermore, studying the involvement of histone modifying enzymes in altering chromatin structure at the promoter region of specific genes will help in understanding epigenetic alteration responsible for the pathophysiology of diseases like cancer, diabetes, asthma and cardiovascular diseases.*

Current Research Areas

Diabetes and its complications:

- Epigenetic modulation of NFAT/mTOR signaling pathway in human podocytes under hyperglycemic condition
- Heat shock proteins involvement in the prevention of diabetes and its associated complications

- Role of PDE4 and ACE2 in the development and progression of diabetic nephropathy by Roflumilast and DIZE

Cardiovascular Diseases:

- Development of DOCA-salt hypertension and the role of AMPK and NFAT in mitigating cardiovascular and renal complications
- Cardiovascular and renal dysfunction in uninephrectomy condition
- Role of local renin angiotensin system (RAS) in atherosclerosis

Asthma:

- Development of murine model of asthma
- Role of ACE2 and NFAT in asthma

Cancer:

- Inhibitors for DNA methylation and histone acetylation in cancer
- Combination therapies with enhanced anti-cancer activity & reduced toxicity in cancer

Nanotoxicology:

- Aptamer mediated drug delivery of various nano-formulations
- Toxicity of nanoparticles involved in drug delivery
- Synthesis of Zinc oxide, Vanadium pentoxide, Selenium, Disulfiram and Gold nanoparticles

AWARDS RECEIVED

OPPI Scientist Award in the year 2011

L to R: Tapan Ray, director general, OPPI, Ranjit Shahani, president, OPPI, Kulbhushan Tikoo, Prof. of Pharmacology and Toxicology, Chief Guest Andrew Witty, global chief executive officer, GSK

nature INDIA

doi:10.1038/nindia.2015.33 Published online 12 March 2015

Aptamers for cancer therapeutics

Researchers Jasmine Kaur and Kulbhushan Tikoo

Scientists from National Institute of Pharmaceutical Research, Mohali, have described the molecular mechanism of an RNA aptamer which specifically targets drug resistant and metastatic cancer cells[1].

Aptamers - single stranded nucleic acids - have emerged as contemporaries to antibodies due to their high affinity for target cells and researchers worldwide are working on aptamer-based drug delivery systems.

The NIPER researchers selected the RNA aptamer through Cell-SELEX process. The aptamer shows high specificity towards its target gefitinib-resistant lung cancer cells and

spares the normal lung cells. They used this aptamer to deliver gefitinib-loaded nanoparticles synthesised earlier[2].

Aptamer conjugated geftinib nanoparticles (GNPs) showed higher internalization and retention within the resistant cell type as compared to normal GNPs. Due to this the anti-cancer activity of the bio-conjugate was also higher. They did not observe any internalization of bio-conjugate within normal lung cells and saw higher efficacy of the delivery system in xenograft mice with tumours.

"The bio-conjugate alleviates tumour growth. It also significantly lowers body weight loss in bio-conjugate treated animals as compared to animals treated with gefitinib and GNPs," says lead researcher Kulbhushan Tikoo.

The researchers used bioinformatic approach to identify the aptamers' target and were intrigued to find that the aptamer was identifying Ets-1, an oncogenic transcription factor, as its target. Through extensive transfection and co-localization assays, they showed that the high specificity of their aptamer towards drug resistant cells was due to the presence of high levels of Ets-1 in these cells.

Their selected aptamer also internalized within other Ets-1 expressing metastatic and drug resistant cancer cells like H23 lung cancer, MDA-MB231 breast cancer and DU-145 prostate cancer cells. The delivery system, they say, is well suited for not only carrying pharmaceutical cargoes within Ets-1 expressing metastatic cancer cells but also for the diagnosis of highly progressive cancer cells.

References

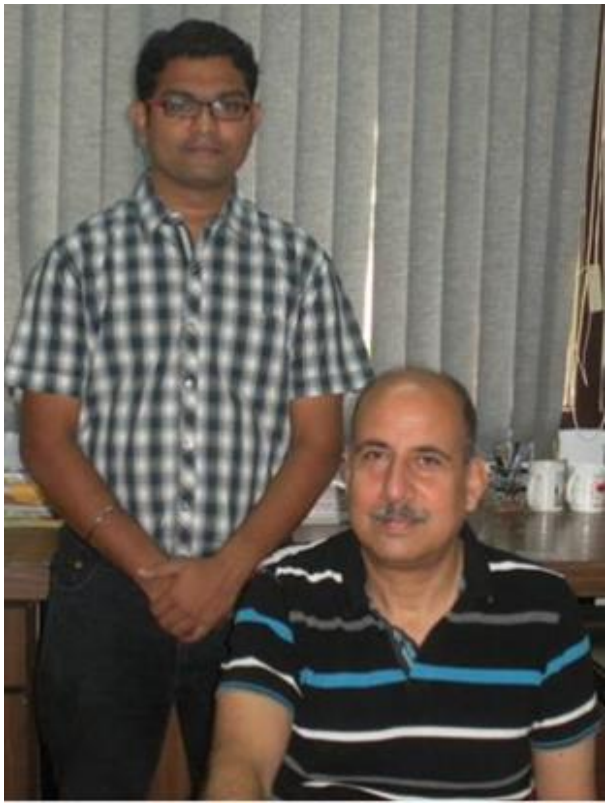
1. Kaur, J. & **Tikoo K**. Ets-1 identified as a novel molecular target of RNA aptamer selected against metastatic cells for targeted delivery of nano-formulation. Oncogene (2015) doi: 10.1038/onc.2014.447

2. Kaur, J. & **Tikoo K**. p300/CBP dependent hyperacetylation of histones potentiates anticancer activity of Gefitinib nanoparticles. Biochim. Biophys. Acta. 1833, 1028-1040 (2013)

doi:10.1038/nindia.2014.69 Published online 26 May 2014

Heat treatment for diabetes

Kulbhushan Tikoo (front) with co-researcher Pinakin Karpe



Mild heat treatment has been shown to suppress diabetic conditions in rats prompting researchers to suggest that it could be used as a treatment protocol for diabetes[1].

The researchers exposed the experimental animals fed on a high-fat diet to 410C heat treatment for 20 minutes once a week. They found that conditions such as hyperglycemia, hyperinsulinemia and hyperlipediema were suppressed in the rats.

Mild heat stress also alters the vascular tone and expression of several vasoprotective genes such as eNOS, SIRT1 and AMPK. The heat stress leads to increase in expression of HSP72

which functions as a chaperone and maintains proper folding of various proteins in stressed condition.

Earlier studies have found that expression of HSP72 was lost in diabetic condition. This suggests that the alteration in HSP72 expression is involved in the pathogenesis of diabetes.

"We were able to induce the HSP72 expression in thoracic aorta of the rats", says lead researcher Kulbhooshan Tikoo of the National Institute of Pharmaceutical Education and Research in Mohali, Punjab. This led to augmentation of the vasoprotective ANG-(1-7)/Mas/ACE2 axis of renin angiotensin system (RAS). Activation of this axis has been shown to buffer the actions of harmful ANG II/AT1/ACE1 axis and improves insulin signalling.

The researchers say therapies stimulating this axis would be helpful to counteract diabetes and associated complications.

References

1. Karpe, P. A. & **Tikoo K**. Heat shock prevents insulin resistance induced vascular complications by augmenting Angiotensin-(1-7) signalling. Diabetes (2014) doi: 10.2337/db13-1267

natureINDIA

Anti-cancer Drug Better in nano-form

Gefitinib, a drug used for treatment of cancer, has been found to have enhanced anti-cancer activity when delivered encapsuled inside nanoparticles. The difference in property arises from the fact that the nanoparticle covered drug acts as a 'histone acetyltransferases' rather than a 'tyrosine kinase inhibitor' which gefitinib is in its free form, new research says[1].

Gefitinib is a widely used drug for treatment of Non-Small Cell Lung Cancer (NSCLC). It is a tyrosine kinase inhibitor, meaning it inhibits the enzyme tyrosine kinase responsible for triggering cancer cells. Researchers have now shown that gefitinib behaves as a histone acetyltransferases (HAT) activator when coated in poly-lactic co-glycolic acid (PLGA) nanoparticles.

The new complex -nano-gefitinib- exhibits completely different anti-cancer mechanism as compared to the free drug, which stalls cell proliferation primarily by inhibiting Epidermal Growth Factor Receptor (EGFR).

The researchers evaluated the molecular mechanism behind this enhanced activity. They found that the nanoparticles "hyperacetylate histone H3 via activation of histone acetyltransferases p300/CBP, which further increases the expression of cell cycle arrest protein p21".

"We were intrigued to observe that a tyrosine kinase inhibitor behaved as a HAT activator merely by choosing a nano-sized transporting vehicle" says Kulbhushan Tikoo lead researcher from National Institute for Pharmaceutical Education and Research, Mohali. The findings suggest that the activity/toxicity profile of drugs may completely change when they are delivered in nano form, he told *Nature India*.

References

1. Kaur J, **Tikoo K**. p300/CBP dependent hyperacetylation of histone potentiates anticancer activity of gefitinib nanoparticles. Biochim Biophys Acta. 2013 May;1833(5):1028-40

natureINDIA

Cracking the histone code

Kulbhushan Tikoo (sitting) with co-researchers

Curcumin, the main ingredient of Indian spice turmeric, provides protection against diabetic nephropathy, a kidney abnormality triggered by diabetes. New research has now pinpointed how this works.

Curcumin plays a role in modifying the histones (proteins that wrap up DNA to form chromatin), in turn bolstering the anti-oxidant defense system of the body; an epigenetic study on rats has concluded[1].

A research team from the National Institute of Pharmaceutical Education and Research (NIPER), Punjab, designed a series of experiments to unravel this protective effect of curcumin. "Curcumin has been used to treat cancer, diabetes and other pathologies. However, little was known regarding its role in bringing about change in histone H3", says lead researcher Kulbhushan Tikoo.

In diabetes, there are changes in the 'histone code' which result in modifying gene expression and lead to the major microvascular complication — diabetic nephropathy. Curcumin was found to decrease the oxidative stress by boosting the anti-oxidant defense system of the body and improving biochemical alterations that resulted in better health.

The team underpinned the role of histone code acting as a prelude to the disease progression and development. The finding could have implications in drug design and developmental programmes targeting diabetes and its complications.

References

1. **Tikoo K**. *et al.* Change in post-translational modifications of histone H3, heat-shock protein-27 and MAP kinase p38 expression by curcumin in streptozotocin-induced type I diabetic nephropathy. Brit. J. Pharmacol. 153, 1225-1231 (2008)

natureINDIA

Fast cure for diabetes

Fasting could be an effective way to control diabetes, says Kulbhushan Tikoo.

Fasting is a well established way of dietary restriction. It involves limiting food and calorie intake below normal levels without reaching malnutrition and can extend the lifespan in most, if not all species, including humans.

Based on this assumption, dietary restriction should prolong not only life span, but also youthfulness and keep at bay diseases associated with lifestyle disorders. In fact, in both rodents and humans, limiting the caloric intake delays many age-associated traits and diseases, including cognitive deterioration and cancer. In addition, dietary restriction can reduce body weight and normalise blood glucose, insulin, and leptin levels in obese animals and humans.

Research[1] carried out at the National Institute of Pharmaceutical Education and Research, Mohali explored the role of intermittent fasting in the progression of diabetic nephropathy and the different underlying mechanisms involved. The observations suggest that alternate day fasting in diabetic animals prevents progression of renal disease. Dietary restrictions also helped reduce tumor formation and increased resistance of neurons to dysfunction and degeneration in experimental models of Alzheimer's, Parkinson's disease and stroke.

Molecular mechanism

The merits of fasting to cure diabetes find mention in ancient Indian Ayurvedic texts such as the Caraka Samhita Sutra. Several ayurvedic practioners in the country still use fasting as one of the treatment protocols in diabetes. As one starves, digestive enzymes inactivate different toxin as well as all patho-physiological factors responsible for progression of the disease. This is how Ayurveda explains the mechanism. However, the different molecular and cellular mechanisms involved in fasting are not completely known.

More recently, several possible molecular mechanisms have been proposed that might explain the beneficial effects of intermittent fasting on aging and disease including reduction in mitochondrial oxyradical production, induction of a cytoprotective cellular stress response, and stimulation of the production of growth factors.

In addition, to these mechanisms, the NIPER study demonstrated that alternate day fasting prevents the decrease in sirtuins (Sir 2) expression in the kidney of diabetic animals during the nephropathy progression. Several reports have shown involvement of sirtuins (a longevity protein) in extending the life span of wide variety of organisms[2].

Two different paradigms to extend life span are widely employed in rat and mice — calorie restriction (CR), in which 30 to 40% less than normal food is allowed for consumption; and intermittent fasting (IF), in which food is given every other day. Out of several possible molecular mechanisms that might explain the beneficial effect of CR or IF, one is increase in expression of Sirtuins. Several reports also show involvement of sirtuins in inflammation, which is involved in number of pathological conditions, including diabetes, cancer, arthritis, asthma, heart disease and neurodegeneratation.

Sirtuins target many proteins that are not histones, they have been demonstrated to bind and deacetylate p53 in vitro and in vivo. The expression of p53 protein in the kidneys of diabetic animals increased as compared to their respective controls. However, the expression of proapoptotic p53 reduced significantly in the kidneys of diabetic rats on IF regimen.

The expression as well as activation of p53 is thought to be mediated by Sir2 dependent deacetylation. They both share an inverse relationship as is evident from the results where the Sir2 expression is decreased and at the same time p53 is upregulated. Further IF decreases the level of caspases-3 and p38 which are involved in apoptosis as compared to diabetic animal kidney and shows its antiapoptotic effect. Although the mechanism by which IF exerts its anti apoptotic effects is yet to be understood in detail but these results suggest a cross talk between Sir2, p53, p38 and caspase-3.

These and other findings may have unique clinical efficacy in preventing the development and progression of diabetic complications in diabetes. In the present scenario in India, there has been a marked change in lifestyle and eating habits of people rendering them more prone to develop different lifestyle disorders like diabetes and metabolic syndrome. Fasting could be a useful intervention for enhancing life span as well as minimising the risk of metabolic disorders.

Past work

A clinical study aimed at increasing exercise combined with diet is able to decrease the incidence of type 2 diabetes[3]. The Indian Diabetes Prevention Programme demonstrated the lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance[4].

As per World Health Organization (WHO), across the world the total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. The maximum absolute increase in the number of people with diabetes will be in India. In 2000, the number of diabetic patients was 31 million and is predicted to go up to 79 million till 2030[5]. India is the capital of the lifestyle disease diabetes.

Of all the abnormalities associated with diabetes, nephropathy or renal failure has became the world's leading cause of chronic and end-stage renal disease[6]. It is associated with structural changes in the glomerulus such as thickening of the glomerular basement membrane and eventually causes progressive hyperfiltration and albuminuria. As the disease progresses, glomerular filtration rate (GFR) declines and leads to end-stage renal disease.

To treat diabetic nephropathy, a variety of therapeutic approaches or treatments are available. While they can slow down the development of the disease, they do not stop the progression of end stage renal failure.

The author is an associate professor in the department of pharmacology and toxicology at the National Institute of Pharmaceutical Education and Research, Punjab, India.

References

1. **Tikoo K**. *et al.* Intermittent fasting prevents the progression of type I diabetic nephropathy in rats and changes the expression of Sir2 and p53. FEBS Lett. 581, 1071-1078 (2007)

PUBLICATIONS

Sr. No.	Publication	Impact Factor 2015
68	Thummuri D, Kumar S, Surapaneni SK, **Tikoo K.,** Epigenetic regulation of protein tyrosine phosphatase PTPN12 in triple-negative breast cancer. Life Sci. 2015 Jun 1;130:73-80. Epub 2015 Mar 25	2.538
67	Kumar S, **Tikoo K.,** Independent role of PP2A and mTORc1 in palmitate induced podocyte death. Biochimie. 2015 May; 112:73-84. Epub 2015 Feb	3.123
66	Choudhary A, Kumar R, Srivastava RB, Surapaneni SK, **Tikoo K.,** & Singh, I. P. (2015). Isolation and characterization of phenolic compounds from Rhodiola imbricata, a Trans-Himalayan food crop having antioxidant and anticancer potential. J Funct Foods, 16, 183-193.	4.48
65	Khan S, Jena G, **Tikoo K.,** Sodium valproate ameliorates diabetes-induced fibrosis and renal damage by the inhibition of histone deacetylases in diabetic rat. Exp Mol Pathol. 2015 Apr; 98(2):230-9. Epub 2015 Jan 7	2.88
64	Tallapragada DS, Karpe PA, **Tikoo K.,** Long standing partnership between insulin resistance and endothelial dysfunction: Role of metabolic memory. Br J Pharmacol. 2015 Mar 30. Epub ahead of print	4.99
63	Khan S, Jena G, **Tikoo K**, Kumar V. Valproate attenuates the proteinuria, podocyte and renal injury by facilitating autophagy and inactivation of NF-κB/iNOS signaling in diabetic rat. Biochimie. 2015 Mar;110:1-16. Epub 2015 Jan 5	3.123
62	Soni, P., Kaur, J., & **Tikoo K.,** (2015). Dual drug-loaded paclitaxel–thymoquinone nanoparticles for effective breast cancer therapy. *Journal of Nanoparticle Research*, *17*(1), 1-12	2.278
61	Kaur J, **Tikoo K.,** Ets1 identified as a novel molecular target of RNA aptamer selected against metastatic cells for targeted delivery of nano-formulation. Oncogene. 2015 Feb 2. [Epub ahead of print].	8.559

60	**Tikoo K**, Patel G, Kumar S, Karpe PA, Sanghavi M, Malek V, Srinivasan K. Tissue specific up regulation of ACE2 in rabbit model of atherosclerosis by atorvastatin: role of epigenetic histone modifications. Biochem Pharmacol. 2015 Feb 1;93(3):343-51. Epub 2014 Dec 4	4.65
59	Trivedi PP, Jena GB, **Tikoo KB**, Kumar V. Melatonin modulated autophagy and Nrf2 signaling pathways in mice with colitis-associated colon carcinogenesis. Mol Carcinog. 2015 Jan 16. [Epub ahead of print].	4.77
58	Aher JS, Khan S, Jain S, **Tikoo K**, Jena G. Valproate ameliorates thioacetamide-induced fibrosis by hepatic stellate cell inactivation. Hum Exp Toxicol. 2015 Jan;34(1):44-55. doi: 10.1177/0960327114531992. Epub 2014 May 8.	1.407
57	Kulkarni A, Kumar GS, Kaur J, **Tikoo K**., A comparative study of the toxicological aspects of vanadium pentoxide and vanadium oxide nanoparticles. Inhal Toxicol. 2014 Nov;26(13):772-88. Epub 2014 Oct 9	2.344
56	Bagul P, Khomane KS, Kesharwani SS, Pragyan P, Nandekar PP, Meena CL, Bansal AK, Jain R, **Tikoo K**, Sangamwar AT. Intestinal transport of TRH analogs through PepT1: the role of in silico and in vitro modeling. J Mol Recognit. 2014 Oct; 27(10):609-17	2.337
55	Kumar GS, Kulkarni A, Khurana A, Kaur J, **Tikoo K**., Selenium nanoparticles involve HSP-70 and SIRT1 in preventing the progression of type 1 diabetic nephropathy. Chem Biol Interact. 2014 Oct 6;223C:125-133. [Epub ahead of print]	2.98
54	Bagul P, Khomane KS, Kesharwani SS, Pragyan P, Nandekar PP, Meena CL, Bansal AK, Jain R, **Tikoo K**, Sangamwar AT. Intestinal transport of TRH analogs through PepT1: the role of in silico and in vitro modeling. J Mol Recognit. 2014 Oct;27(10):609-17. doi: 10.1002/jmr.2385. (Impact factor: 2.337)	2.337
53	**Tikoo K**, Lodea S, Karpe PA, Kumar S. Calorie restriction mimicking effects of roflumilast prevents diabetic nephropathy. Biochem Biophys Res Commun. 2014 Aug 8;450(4):1581-6. doi: 10.1016/j.bbrc.2014.07.039. Epub 2014 Jul 15.	2.28
52	Gupta C, Kaur J, **Tikoo K**. Regulation of MDA-MB-231 cell proliferation by GSK-3β involves epigenetic modifications under high glucose	3.372

	conditions. Exp Cell Res. 2014 May 15;324(1):75-83. doi: 10.1016/j.yexcr.2014.03.019. Epub 2014 Apr 1.	
51	Sharma V, **Tikoo K**. Stage-specific quantitative changes in renal and urinary proteome during the progression and development of streptozotocin-induced diabetic nephropathy in rats. Mol Cell Biochem. 2014 Mar;388(1-2):95-111. doi: 10.1007/s11010-013-1902-5. Epub 2013 Nov 27.	5.036
50	Karpe PA1, **Tikoo K**. Heat shock prevents insulin resistance-induced vascular complications by augmenting angiotensin-(1-7) signaling. Diabetes. 2014 Mar;63(3):1124-39. doi: 10.2337/db13-1267. Epub 2013 Nov 22.	8.1
49	Jain S1, Rachamalla M, Kulkarni A, Kaur J, **Tikoo K**. Pulmonary fibrotic response to inhalation of ZnO nanoparticles and toluene co-exposure through directed flow nose only exposure chamber. Inhal Toxicol. 2013 Nov;25:703-13. doi:10.3109/08958378.2013.839765.	2.344
48	Bendale DS, Karpe PA, Chhabra R, Shete SP, Shah H, **Tikoo K**. 17-β Estradiol prevents cardiovascular dysfunction in Post-menopausal Metabolic Syndrome by involving SIRT1/AMPK/H3 acetylation.. British Journal of Pharmacology. 2013 Jul 5. doi: 10.1111/bph.12290.	5.06
47	Gupta C, **Tikoo K**. High glucose and insulin differentially modulates proliferation in MCF-7 and MDA-MB-231 cells. Journal of Molecular Endocrinology. 2013 Jun 29;51(1):119-29.	3.57
46	Vekariya KK, Kaur J, **Tikoo K**. Alleviating anastrozole induced bone toxicity by selenium nanoparticles in SD rats. Toxicology and Applied Pharmacology. 2013 Apr 15;268(2):212-20.	4.1
45	**Tikoo K.**, Anti-cancer Drug Better in nano-form Nature India, Doi:10.1038/nindia.2013.32.	
44	Kaur J, **Tikoo K**. p300/CBP dependent hyperacetylation of histone potentiates anticancer activity of gefitinib nanoparticles. Biochim Biophys Acta. 2013 May;1833(5):1028-40.	5.5
43	Kumar L, Meena CL, Pawar YB, Wahlang B, **Tikoo K**, Jain R, Bansal AK. Effect of counterions on physicochemical properties of prazosin salts. AAPS PharmSciTech. 2013 Mar;14(1):141-50.	1.58

42	Kaur J, **Tikoo K**. Evaluating cell specific cytotoxicity of differentially charged silver nanoparticles.Food and Chemical Toxicology. 2013 Jan;51:1-14.	3.02
41	Gupta J, Kumar S, Li J, Krishna Murthy Karuturi R, **Tikoo K**. Histone H3 lysine 4 monomethylation (H3K4me1) and H3 lysine 9 monomethylation (H3K9me1): distribution and their association in regulating gene expression under hyperglycaemic/hyperinsulinemic conditions in 3T3 cells. Biochimie. 2012 Dec;94(12):2656-64.	3.14
40	Khomane KS, Nandekar PP, Wahlang B, Bagul P, Shaikh N, Pawar YB, Meena CL, Sangamwar AT, Jain R, **Tikoo K**, Bansal AK. Mechanistic insights into PEPT1-mediated transport of a novel antiepileptic, NP-647. Molecular Pharmaceutics. 2012 Sep 4;9(9):2458-68.	4.57
39	Gupta J, **Tikoo K**. Involvement of insulin-induced reversible chromatin remodeling in altering the expression of oxidative stress-responsive genes under hyperglycemia in 3T3-L1 preadipocytes. Gene. 2012 Aug 10;504(2):181-91.	2.37
38	Rehni AK, Singh N, Rachamalla M, **Tikoo K**. Modulation of histone deacetylase attenuates naloxone-precipitated opioid withdrawal syndrome. Naunyn Schmiedebergs Arch Pharmacol. 2012 Jun;385(6):605-19.	2.14
37	Wahlang B, Kabra D, Pawar YB, **Tikoo K**, Bansal AK. Contribution of formulation and excipients towards enhanced permeation of curcumin. Arzneimittelforschung. 2012 Feb;62(2):88-93.	0.722
36	Khatik GL, Kaur J, Kumar V, **Tikoo K**, Nair VA. 1,2,4-Oxadiazoles: a new class of anti-prostate cancer agents.. Bioorganic Medicinal Chemistry Letters. 2012 Mar 1;22(5):1912-6.	2.33
35	Patel RS, Rachamalla M, Chary NR, Shera FY, **Tikoo K**, Jena G. Cytarabine induced cerebellar neuronal damage in juvenile rat: correlating neurobehavioral performance with cellular and genetic alterations. Toxicology. 2012 Mar 11;293(1-3):41-52.	4.01
34	Vekariya KK, Kaur J, **Tikoo K**. ERα signaling imparts chemotherapeutic selectivity to selenium nanoparticles in breast cancer. Nanomedicine. 2012 Oct;8(7):1125-32.	6.93

33	Karpe PA, Gupta J, Marthong RF, Ramarao P, **Tikoo K**. Insulin resistance induces a segmental difference in thoracic and abdominal aorta: differential expression of AT1 and AT2 receptors. Journal of Hypertension. 2012 Jan;30(1):132-46.	4.1
32	Mahajan UM, Gupta C, Wagh PR, Karpe PA, **Tikoo K**. Alteration in inflammatory/apoptotic pathway and histone modifications by nordihydroguaiaretic acid prevents acute pancreatitis in swiss albino mice. Apoptosis. 2011 Nov;16(11):1138-49.	4.2
31	Gopal L. Khatik, Jasmine Kaur, Varun Kumar, Kulbhushan Tikoo, P. Venugopalan, Vipin A. Nair, Aldol derivatives of Thioxoimidazolidinones as potential anti-prostate cancer agents, European Journal of Medicinal Chemistry 46 (2011) 3291-3301.	3.5
30	**Tikoo K**, Surse VM, Gupta J, Esculetin induced changes in Mmp-13 and Bmp-6 gene expression and histone H3 modifications attenuate development of glomerulosclerosis in diabetic rats, Journal of Molecular Endocrinology. 2011 Jun 9;46(3):245-54.	3.57
29	**Tikoo K**, Sane MS, Gupta C, Tannic acid ameliorates doxorubicin-induced cardiotoxicity and potentiates its anti-cancer activity: Potential role of tannins in cancer chemotherapy, Toxicology and Applied Pharmacology 2010 Dec 29.	4.1
28	Gaikwad AB, Gupta J, **Tikoo K** (2010).Epigenetic changes and alteration of Fbn-1 and Col3A1 gene expression under hyperglycemic and hyperinsulinemic conditions. Biochemical Journal. 2010 Nov 12;432(2):333-41	4.7
27	Gupta J, Gaikwad AB, **Tikoo K** (2010).Hepatic expression profiling shows involvement of PKC epsilon, DGK eta, Tnfiap and Rho kinase in type 2 diabetic nephropathy rats. Journal of Cellular Biochemistry. Nov 1;111(4):944-54.	3.1
26	Sayyed SG, Gaikwad AB, Lichtnekert J, Kulkarni O, Eulberg D, Klussmann S, **Tikoo K**, Anders HJ. Progressive glomerulosclerosis in type 2 diabetes is associated with renal histone H3K9 and H3K23 acetylation, H3K4 dimethylation and phosphorylation at serine 10. Nephrology Dialysis Transplantation, 2010, January 12.	3.37

25	Mulay SR, Gaikwad AB, **Tikoo K**. Combination of Aspirin with Telmisartan suppress the augmented TGF-beta/smad signaling during the development of Streptozotocin induced type I diabetic nephropathy. Chemico-biological Interactions, 2010, March 16.	2.96
24	Gaikwad AB, Sayyed SG, Lichtnekert J, **Tikoo K**, Anders HJ (2010). Renal Failure Increases Cardiac Histone H3 Acetylation, Dimethylation, and Phosphorylation and the Induction of Cardiomyopathy-Related Genes in Type 2 Diabetes. American Journal of Pathology 176(3): 1079.	5.0
23	**Tikoo K**, Ali IY, Gupta J, Gupta C. 5-Azacytidine prevents cisplatin induced nephrotoxicity and potentiates anticancer activity of cisplatin by involving inhibition of metallothionein, pAKT and DNMT1 expression in chemical induced cancer rats. Toxicology Letters. 2009, article in press	3.2
22	**Tikoo K.**, Fast Cure for Diabetes. Nature India, Doi:10.1038/nindia.2009.155.	
21	Kabra DG, Gupta J, **Tikoo K.**, Insulin induced alteration in post-translational modifications of histone H3 under a hyperglycemic condition in L6 skeletal muscle myoblasts. Biochim Biophys Acta. 2009 Jun; 1792(6):574-83.	4.9
20	**Tikoo K**, Kumar P, Gupta J. Rosiglitazone synergizes anticancer activity of cisplatin and reduces its nephrotoxicity in 7, 12-dimethyl benz{a}anthracene (DMBA) induced breast cancer rats. BMC Cancer. 2009 Apr 8; 9:107.	3.33
19	Chandak P.G., Gaikwad, A.B. & **Tikoo K.**, Gallotannin, Ameliorates the Development of Streptozotocin Induced Diabetic Nephropathy by Preventing the Activation of PARP. Phytotherapy Research. 2009 Jan;23(1):72-7	2.068
18	**Tikoo K.**, Cracking the histone code. Nature India, Doi:10.1038/nindia.2008.159.	
17	**Tikoo K**, Roshan Lal Meena, Dhiraj Kabra and Anil Bhanudas Gaikwad (2008) Change in post-translational modifications of histone H3, HSP-27 and p38 expression by curcumin in diabetic nephropathy. British Journal of Pharmacology. 2008 153(6):1225-31	5.01
16	**Tikoo K**, Anupama Tamta and Anil Bhanudas Gaikwad (2008) Tannic	3.2

	acid prevents Azidothymidine (AZT) induced hepatotoxicity and genotoxicity along with change in expression of PARG and histone H3 acetylation Toxicology Letters. 2008;177(2):90-6	
15	**Tikoo K**., Singh K., Kabra, D.G., Sharma, V. & Gaikwad, A.B. 2008. Change in histone H3 phosphorylation, MAP kinase p38, SIR 2 and p53 expression by resveratrol in preventing streptozotocin induced type I diabetic nephropathy. Free Radical Research 2008 Apr;42(4):397-404.	3.28
14	**Tikoo K.**, Tripathi, D.N., Kabra, D.G., Sharma, V. & Gaikwad, A.B. (2007). Intermittent fasting prevents the progression of type I diabetic nephropathy in rats and changes the expression of Sir2 and p53. FEBS Letters, 581, 1071-8.	3.6
13	**Tikoo K**. Bhatt, D.K., Gaikwad, A.B., Sharma, V. & Kabra, D.G. (2007). Differential effects of tannic acid on cisplatin induced nephrotoxicity. FEBS Letters, May15;581(10):2027-35	3.6
12	Sharma, G., Italia, J.L., Sonaje, K., **Tikoo K**. & Ravi Kumar, M.N. (2007). Biodegradable in situ gelling system for subcutaneous administration of ellagic acid and ellagic acid loaded nanoparticles: Evaluation of their antioxidant potential against cyclosporine induced nephrotoxicity in rats. Journal of Controlled Release, 118, 27-37.	7.6
11	Garkhal, K., Verma, S., **Tikoo K**. & Kumar, N. (2007). Surface modified poly(L-lactide-co-epsilon-caprolactone) microspheres as scaffold for tissue engineering. J Biomed Mater Res A, 82(3):747-56.	2.8
10	Italia, J.L., Bhatt, D. k., Bhardwaj, V., **Tikoo K.** & Ravi kumar, M.N.V. (2007). PLGA nanoparticles for oral delivery of cylcosporine: Nephrotoxicity and pharmacokinetic studies in comparison to Sandimmune Neoral. Journal of Controlled Release, Jun 4;119(2):197-206.	7.6
9	Sonaje, K., Italia, J.L., Sharma, G., Bhardwaj, V., **Tikoo K.** & Ravi kumar, M.N.V. (2007). Development of biodegradable nanoparticles for oral delivery of ellagic acid and evaluation of their antioxidant efficacy against cyclosporine A-induced nephrotoxicity in rats. Pharmacology Research, May;24(5):899-908.	2.752
8	Kalra S, Jena G, **Tikoo K**, Mukhopadhyay AK Preferential inhibition of	1.77

	xanthine oxidase by 2-amino-6-hydroxy-8-mercaptopurine and 2-amino-6-purine thiol.BMC Biochemistry. 2007 May 18; 8:8	
7	Monks, T.J., Xie, R., **Tikoo K**. & Lau, S.S. (2006). Ros-induced histone modifications and their role in cell survival and cell death. Drug Metab Rev, 38, 755-67.	5.5
6	Jain, M., Vangapandu, S., Sachdeva, S., Singh, S., Singh, P.P., Jena, G.B., **Tikoo K**., Ramarao, P., Kaul, C.L. & Jain, R. (2004). Discovery of a bulky 2-tert-butyl group containing primaquine analogue that exhibits potent blood-schizontocidal antimalarial activities and complete elimination of methemoglobin toxicity. J Med Chem, 47, 285-7.	5.6
5	Dong, J., Ramachandiran, S., **Tikoo K**., Jia, Z., Lau, S.S. & Monks, T.J. (2004). EGFR-independent activation of p38 MAPK and EGFR-dependent activation of ERK1/2 are required for ROS-induced renal cell death. Am J Physiol Renal Physiol, 287, F1049-58.	4.42
4	**Tikoo K**., Lau, S.S. & Monks, T.J. (2001). Histone H3 phosphorylation is coupled to poly-(ADP-ribosylation) during reactive oxygen species-induced cell death in renal proximal tubular epithelial cells. Mol Pharmacol, 60, 394-402.	4.8
3	**Tikoo K**., Gupta, S., Hamid, Q.A., Shah, V., Chatterjee, B. & Ali, Z. (1997). Structure of active chromatin: isolation and characterization of transcriptionally active chromatin from rat liver. Biochem J, 322 (Pt 1), 273-9	4.7
2	**Tikoo K**. & Ali, Z. (1997). Structure of active chromatin: covalent modifications of histones in active and inactive genes of control and hypothyroid rat liver. Biochem J, 322 (Pt 1), 281-7.	4.7
1	**Tikoo K**., Hamid, Q.A. & Ali, Z. (1997). Structure of active chromatin: higher-order folding of transcriptionally active chromatin in control and hypothyroid rat liver. Biochem J, 322 (Pt 1), 289-96.	4.7

Projects sanctioned from sources other than Department of Pharmaceuticals

Sr No.	Title of Project	Funding Agency	Amount	Duration
1.	Epigenetic changes during hyperglycemia induced oxidative stress and its role in modulating expression of genes (diabetogenes) involved in pathogenesis of diabetes	Department of Biotechnology, India.	44.798 lakhs	2010-2013
2.	Toxicity screening of nanoparticles used for drug delivery	Department of Science and Technology, India	3.2 Crores	2008-2011
3.	Regulatory Toxicology-development of GLP-certified facility for toxicological screening of new chemical entities	Department of Science and Technology, India	1.3 Crores	2006-2008
4.	Role of Histone Modifications and its Inhibitors in Reactive Oxygen species (ROS) –Induced Cell-Death	Department of Biotechnology, India.	25 lakhs	2003-2007

PATENTS

Number of patents: 7