Research Journal of Recent Sciences _____ ISSN 2277-2502
Vol. 3**(IVC-2014),** 6-15 **(2014)** *Res. J. Recent. Sci.*

Revolutionized strength of future Biomedicine Revealed: Nanolipomedicines

Sharma Meenu
Pacific University, Udaipur, INDIA

Available online at: www.isca.in, www.isca.me
Received 27th May 2014, revised 16th July 2014, accepted 24th August 2014

Abstract

Passing time has seen numerous developments in the computational approaches and applications. All this has shown a specialized positive impact in the field of Biomedicine and lead to encouragement of interdisciplinary fields like medical informatics, bio-informatics, nano-technology, nano-informatics, computational biology, system biology, etc. Present work embraces the analytics of the advancements and unearthing across the most deadly diseases in the world. Major emphasis is on the improvements in the drug delivery methods to ensure site-specificity and effectiveness of the potential drugs. It is the most important aspect of the present targeted therapies is the drug delivery vehicles. Paper revolves around the characteristics of an ideal drug delivery system. Is it Efficiency? Biocompatibility? Or just Nonimmunogenicity? Yes, here drug-carriers are on the spotlight. Additionally we also focused the deciding factors like drug circulation time, its ADMET aspects and chemical descriptors that are the indispensable part of a drug-carrier system. In the end publication survey results provides a suitable podium to present work. The possibilities of novel developments offer the clear cut proof of increasing popularity of biological lipid vesicles and nano-scale drug delivery systems. Citations involve current market and clinical status of such systems in our present day RandD and pharma-market.

Keywords: Nanotechnology, computational biology, drug delivery systems, liposomes, nano-liposomes, nano-informatics, bioinformatics.

Introduction

Exploration and understanding of scientific mechanisms is very helpful in understanding most of the complex biological phenomenon. The rising necessity and need to understanding the hidden facts has given rise to numerous fields and disciplines. Earlier scientific interests revolved around some direct disciplines like botany, zoology, mathematics and chemistry as the most eminent disciplines and later computer applications showed a new direction. With time complexity of tasks lead to the emergence of novel disciples that could answer various multifarious phenomenon of biological world. Time has seen expansion of biochemistry, pharmacology, molecular biology. Multidisciplinary and interdisciplinary research have mined new ground such as health science, biology, molecular biology, microbiology, biotechnology, bioinformatics, nano-informatics, nanotechnology, system biology, statistics, computer science, computational biology[1].

Everywhere bioinformatics is seen blending molecular biology with computer science in a variety of ways. The informatics provided the essential strength required for understanding genomic information. This in-turn opens new horizons to understand human diseases and identify molecular targets for the process of drug discovery. Computational biology offers fundamental explanation and has given new direction to the research. Novel means have been developed for molecular modelling, pattern recognition, simulation and analysis of noisy biological data. Some of these are miRNA profiling of human tumorigenesis, NGS applications, biomarker discovery, insilico methods of drug designing, sequencing projects, clinical research, and cancer phylogenetics[2].

With transforming time, trend and method for pursuing research also changes in many facets. For instance let's talk about a research study that involves exploring some disease condition and bringing a corresponding drug to market. This process is lot of time, money and energy consuming. And at last after spending years in research one may end into an anonymous result or some surprising results that may or may not carry some significant value. Now this trend has been revolutionized with the emergence of IT field. Software development has enabled the life science researchers to predict the outcomes of any said process with much reliability and there by decreased the amount of unpredictable results.

Medicine and medical biology has observed a new upheaval after insilico approaches of drug designing. Novel application of nano-sized particles are coming to light for varied biotechnological applications. With time these nano-sized materials have emerged as nano-diagnostic tools in the hands of biotechnology, medical biology and medicine[2] as are illustrated in figure-1. Research groups observer Nanotechnology as the next broad revolution in medicine[3]. Every year numerous ideas for using nano-materials are applied for the development of biosensors. Ventures are also busy in finding new market opportunities using such technologies[4].

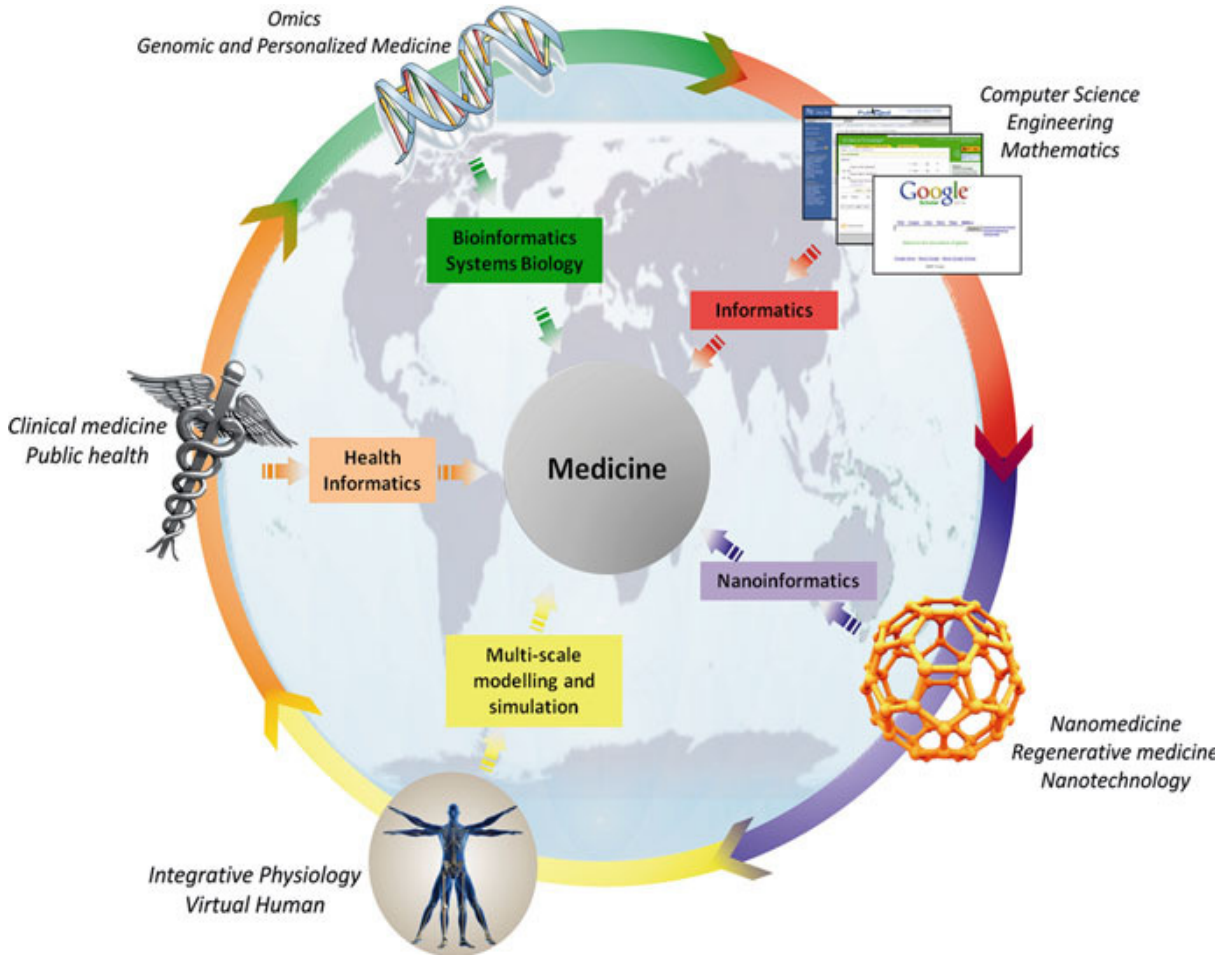

Figure-1
Relationship among emerging trends in science and medicine

Surveys reveal the fact that the applications involving nanomaterials in biotech field involves a very complex section. These nano-particles vary in numerous aspects, namely their potentiality, synthesis, characterization, application, limitations, etc.

Relation among bioinformatics, drug targets and biomedicines: Bioinformatics plays a major role in prediction of drug targets, biomarkers that lead to the development of potential biomedicines. Studies and evidences has indicated that for systematic understanding of cellular behaviour and mechanisms one should move to micro-environment specially for better understanding of abnormal cell growth in tumour genesis. The concept further gets diversified with the picture of complex and vivid heterogeneous cell population that exist within[5]. Nano-diagnosis is applicable to intensify the research studies. Molecular signatures of microenvironment are paid special attention aided with genomics and proteomics. Even after finding a potential drug target the most challenging task is to deliver drug or medicine to right site and in optimal condition. A medicine can be introduced by numerous means. Here comes the significance of drug carrier molecules. Nano-sized therapeutic agents are the best option and can carry peptides, small molecules, RNA, DNA or drug fragments that have novel applications in various drug therapies including tumour therapies[6].

Material and Methods

Microscale biological molecules (liposomes): Liposomes are a micro-sized globular vesicle that retains an aqueous central core enveloped inside lipid bilayer[7]. The concept to exploit liposomes, the cellular vesicles, as drug carrier was introduced due its structural and compositional similarity with the cellular membranes. These have now developed as potential drug carrier molecules that exhibit minimal drug toxicity and higher antitumor efficacy. The trend has started with Doxorubicin liposomal injections and currently many more anticancer drugs are encapsulated in liposomes. Liposomes support the clinical study concepts in several aspects. As an anticancer drug carrier system it has undergone several modifications. It is now a part of widespread development programs to fulfil the growing expectations including the novel liposomal synthesis and formulations[8].

Liposomes possess many benefits when used as drug or small molecule carriers systems. Firstly it increases the possible routes for the administration such as intravenous, inhalation, derma-application, etc. secondly such a means also reduces the toxic effect on the healthy tissues as it gets selectively absorbed by abnormal cells. Thirdly it has ability to provide proper environment to phobic, philic, or amphiphalic drugs. Fourthly its biological composition makes this moiety Biocompatible, biodegradable and least immunogenic. Fifthly, but not the least it provides the option of surface modification with various ligands to increase the target specific binding[9].

Liposomal Drug Delivery Systems: Liposomes have attracted the world since liposomes first came to light in 1965. Today liposomes are vastly applied as unique molecules in drug delivery strategies owing to their unique characteristics[7]. Their strength lies in their structural organization and versatile physicochemical descriptors. Further encouragement is provided by dual character of liposomes as hydrophobic and hydrophilic drug carriers. All this resulted in the wider use of liposomes as drug carrier molecules soon as early as 1970's. However the fact that liposomes belong to the 1st generation carriers comes to light when US FDA approved it and was successfully used to deliver doxorubicin to treat acquired immunodeficiency syndrome. Currently they are utilized as nanoparticles frequently employed as antimicrobial drug delivery systems. Liposomes own the speciality that within a cell population they can be precisely target specific. Liposomes are biodegradable, and provide a controlled drug release environment[8].

Despite numerous advantages like biocompatibility and being safe, the major drawback of these carrier systems is their poor stability in plasma. They also have shorter half life in plasma but this property is widely used for the anti-microbial drugs to treat tuberculosis. In order to increase the circulation time and self-life of liposomes in blood several lipid compositions like polyethylene glycol (PGE) coated and sterically established liposomes are being used. Whether the actual mechanism has not been yet fully understood still PGE has added to the success story of liposomes. Liposomal surfaces are frequently decorated with small molecules such as antibodies to enhance target specific binding and drug delivery.

Traditionally they are used to assist poorly soluble drugs or therapeutic agents for administration. Amphotericin B is a well known example of marketed drug where this principle was utilized for intravenous infusion[10]. These vesicles are actively removed from circulation by macrophages present in reticulo-enthelial system (liver, spleen, bone-marrow). Immuno-liposomes having surface decorated by catalytic enzymes responsible for the activation of pro-drug has also been designed[10].

Nanoscale and significance of Blood brain barriers: Nano-particles constructs possess a very exclusive substantial and element characteristics associated with 1-100nm size. Biological molecules like antibodies, proteins, receptors, nucleic acids all fall in nanometer range[11]. This biomimetic feature, high degree of surface to volume ration and likelihood to transform their assets make them a commanding tool[12-13]. Nanotechnology is drastically changing prototype for drug delivery and widely evolving technology owing to its small size. Nanoscale provided the greater possibilities for developing novel perceptions for prevention, diagnosis and treatment of numerous conditions. Liposomes are great for carrying nuclic acids, small molecules and drugs although with certain adjoining and inevitable limitations[14]. Usually Therapy limitations are met when medicines cannot cross BBB and delivered to various types of tumors like glioblastoma. Yes here we lay stress on the nanoscale and its potential advantage for delivering drugs across blood brain barriers. The nanoscaled chemical design greatly affects the permeability and functions to overcome the BBB with potential applications in cancer therapies[1].

Liponanosomes: Lipid vesicles in nano scale: Liposome preparations with a mean diameter falling in nanometer range constitute liposomes in nano scale or simply nano-liposomes. Here we combine the properties of two great moieties. Liposome nanoparticles demonstrate numerous properties likepeculiar small-size, high reactivity, higher surface: mass ratio that lead to obviously large applications[5]. In a related study a liponanosome was developed that constitute a Lipid-Calcium-Phosphate (LCP) nanoparticle that practically pools the chemo-therapy with gene-therapy. The study was a novel application in which a chemo-drug, gemcitabine monophosphate (GMP), and siRNA that are particular to the undruggable cMyc oncogene (cMycsiRNA) was encapsulated into a single nanoparticle. This nanoliposome has achievedstrong anti-tumor activity. Additionally Co-encapsulation of a chemo-therapeutic agent and oncogene-modulating siRNA proved to be effective in real-time disruption of varied anti-cancer pathways that is truly responsible for higher therapeutic efficacy and lesser toxicity[15].

Blood Brain Barrier: a major hurdle in medication of neurological disorders: Blood Brain Barrier plays a central role to preserve neuronal integrity by regulating its inner biochemical environment. It adds up a hurdle in medication process limiting the delivery of beneficial drugs to nervous system. The only option left is transporting medicines through the endothelial cells and transverse them through the tight junctions. The fact that only drug should pass through endothelial cells, needs lot of attention and study. Blood Brain Barrier allows only small molecules to pass it and enter the Central Nervous System. But the hard fact is that the drugs for neurological treatment have large sizes. So the only left paradigm is the utilization of liposomes as nanocarriers for potential drug delivery systems to overcome their individual limitations[16].

In earlier studies a barrier was concluded to lie between blood and CSF[17]. and the term Blood Brain Barrier was put forward by Lewandowsky[18]. Blood Brain Barrier consist of lining of

endothelial cells in brain and spinal cord and cells likes pericytes, microglial cells, star-shaped astrocytes[19-21]. This barrier is demonstrated by all animals that possess advances nervous system[22]. yet some glial cells figure-out such a barrier in fish, molluscs and other insect species[23].

The current challenge in medication therapy is to cross blood brain barrier to deliver drugs to brain parenchyma. It has been observed that Blood brain barrier allows only low molecular weight lipophilic moieties with molecular weight lying between 400 to 500 Da to transverse to parenchyma cells of brain[24, 25]. These facts made the drug delivery to brains a big challenge. And because of poor brain penetration rate hardly 10% of the therapeutic agents enter clinical trials[26]. Liposomal drug delivery system will definitely have great application in cancer therapeutics[27].

Nano-Liposomal Case Studies: The miscellany of nano-size particles with flexibility in shapes and range of sizes creates a novel prototype of therapies that are flexible and work well against most tough cancer diseases[14]. Nano-technological systems has arise as quite useful tools for probe diagnostics and therapeutic delivery to brain with reduced toxic side effects and improved drug positive effects. Drug delivery across BBB is the central point of attraction throughout nano-carrier development. Researchers are attracted towards liposomes/micelles, lipid-based/polymeric nanoparticles when exploring biomedicines[28].

Nano-liposomal technology for ocular drug delivery to retina: The promising technology is employed to deliver drug delivery to retina with the aim to get better pharmacokinetic characteristics of drug clearance. A nanoscale version was developed from an anionic, cholesterol-blend liposome that encapsulates minocycline therapeutic levels. This study also demonstrated a 80nm stable liposome that encapsulates minocycline with 2% to 3% of loading material. Significantly 40% of encapsulated minocycline get delivered to retina via nontoxic nano-liposomes with a sub-conjunctival injection. The transcriptomic and proteomic biomarker panels provided the efficacy of the drug delivery[29].

PEP02 improves pharmacokinetic properties for pancreatic cancer: Irinotecan sucrossfacteen encapsulated in a liposomal delivery is known as PEP02 (MM-398). Irinotecan basically is a topoisomerase-1 inhibitor which is presently employed for cancer treatment. The preclinical studies have shown to exhibit superior pharmacokinetics and biodistribution of SN-38 and irinotecan. PEP02 was found optimally acceptable with expected and easily superviseable toxicity in most of the patients.The curative effects of liposome-encapsulated anticancer drugs namely, cytarabine, doxorubicin, daunorubicin are well versed[30].

EuC-NLS improve ALS for osteoporosis treatment: ALS is the Alendronate sodium a very common drug salt employed to fight osteoporosis condition. In real time framework ALS faces numerous hurdles like a very poor bioavailability of 0.6%, a very complicated usage instructions and oesophageal ulcers are to name a few. The research was aimed to formulate enteric-coated nano-liposomes to overcome such shortcomings of ALS administration. Finally EuC-NLS developed within the range of 70-150nm with PC:CH:Lec:dicetyl phosphate (4:3:1:1) defy the ALS release in acidic medium and increased the 12fold bioavailability and a lower dose administration avoided the oesophageal ulcers[31].

LCNs strengthened BAI oral bioavailability: In this study diethyl ether injection method was used to prepare Baicalein (BAI) containing Long-circulating nanoliposomes (LCNs) in which carrier ingredients were cholesterol (CHOL) and Soybean phosphatidylcholine (SPC). These LCNs loaded with BAI fall within 709nm diameter and have encapsulation efficiency 41.5 ± 4.77%. It was found that BAI-loaded LCNs improved the pharmacokinetic properties and highly stable in phosphate-buffered saline at 4 °C near pH 7.4. The encapsulated BAI exhibited 4.52 times better BAI oral bioavailability and suggests the new direction in drug delivery paradigm[32].

Lipo-plexes as Nucleic Acid Delivery Systems: The lipoplexes is a novel application of cationic liposomes for site directed nucleic acids delivery. Lipoplexes are least-toxic, nonimmunogenic and involve a very simple methodology. These facts add to the potential breakthrough in the field of gene-transfer therapy. Now a day's vivid categories of cationic lipids have been employed for the synthesis of lipoplexes to bring major advancement in therapy[33,34,35].

Results and Discussion

Nano-size particles are bringing new direction to potential drug, pharma and medication market. During the whole research study the drugs and their target specific medication delivery is kept focused. Studies revealed that bioavailability, toxicological, pharmacokinetics factors are the most common descriptors that attracted the world wide scientific community while switching to any novel voyage and study. The success story of micro and nano-sized particles is supported by the publication survey done using GoPubmed[36]. Figure 2, 3 and 4 presents the statistical analysis of references for related key terms studied for popularity of publications as revealed by GoPubmed.

Nanotechnology is hastily sprouting and significantly shifting the drug delivery towards a new direction. In tumor research we are designing multifunctional nanoparticles to enhance direct or indirect tumor targeting[14]. Improvements in research must focus the difficulties faced in early tumor detection along with special consideration to multidrug resistance subtleties. Additionally cancer research that aims at immunogenic considerations of current treatment and variation in cell-specific treatment will prove to be an asset[37, 38].

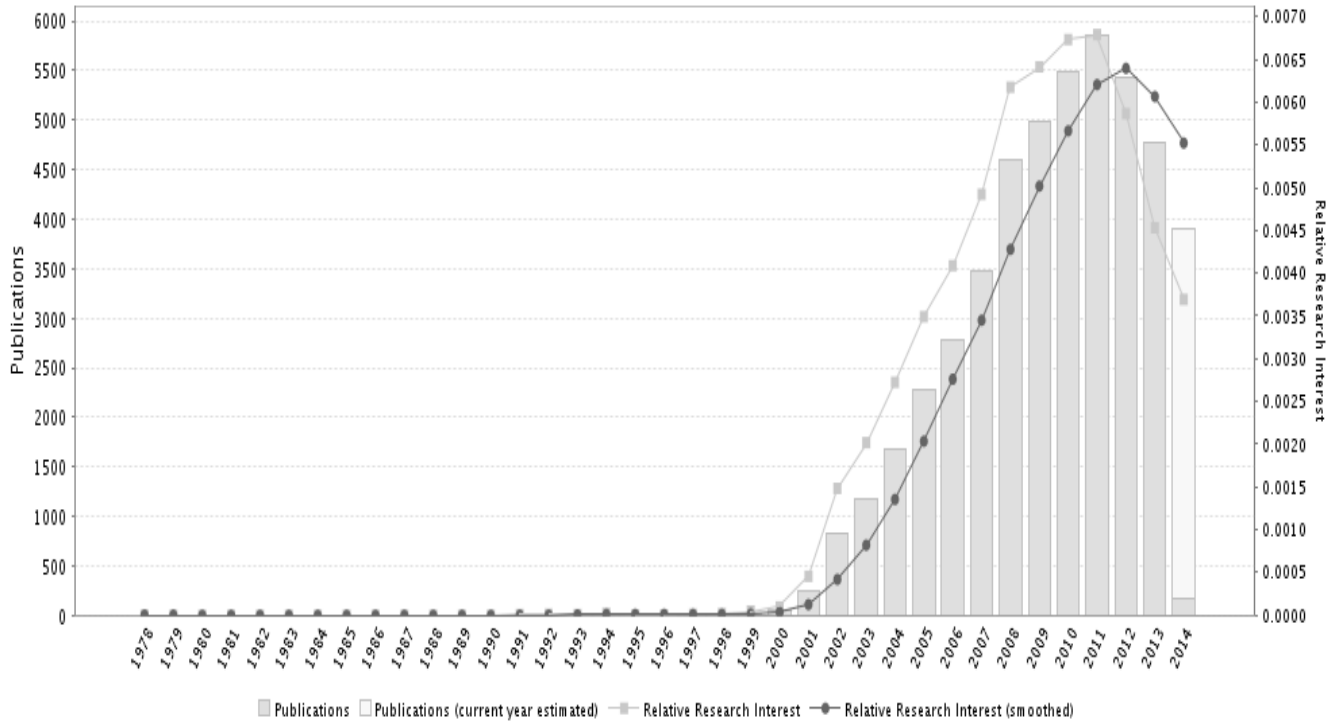

Figure-2(a)
Survey results on nanotechnology

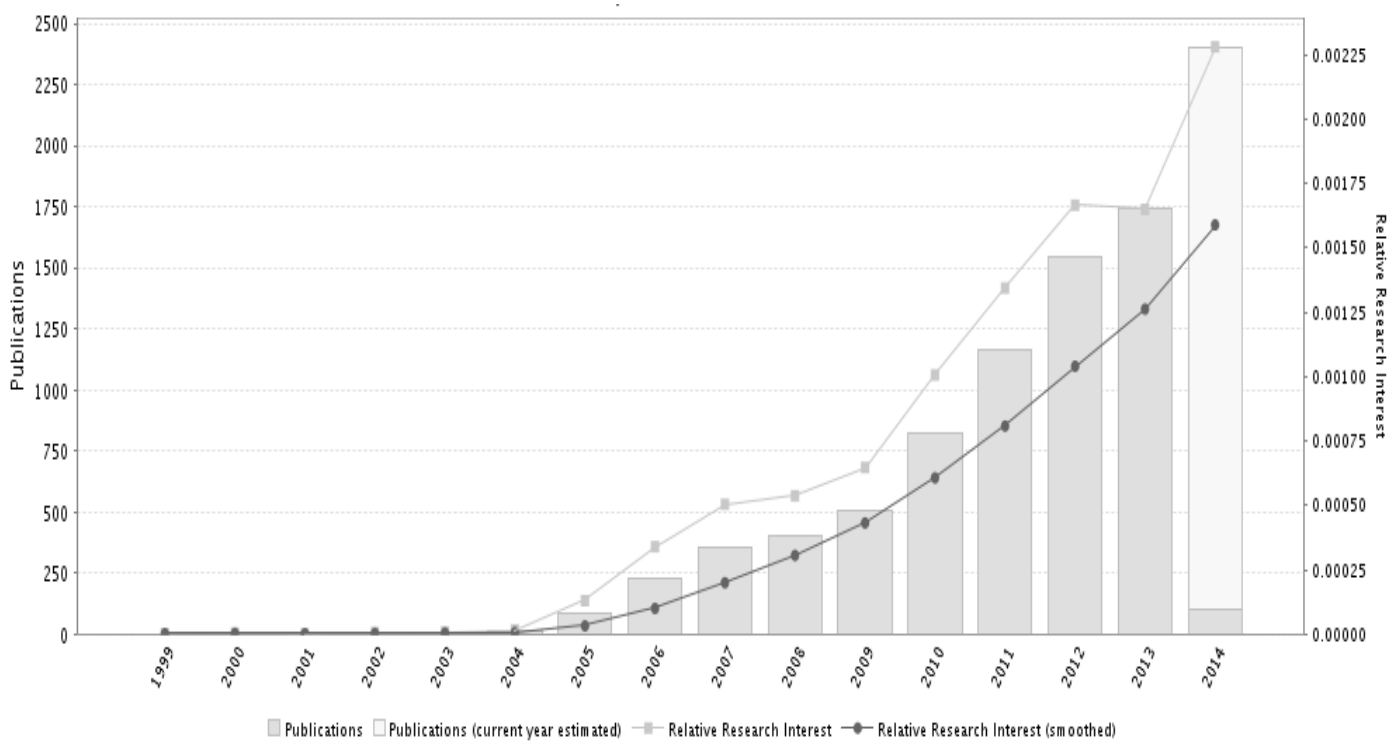

Figure-2(b)
Survey results on Nanomedicine

Nanotechnology alone has lost research interests but application of nano prospects in medicine has been constantly rising

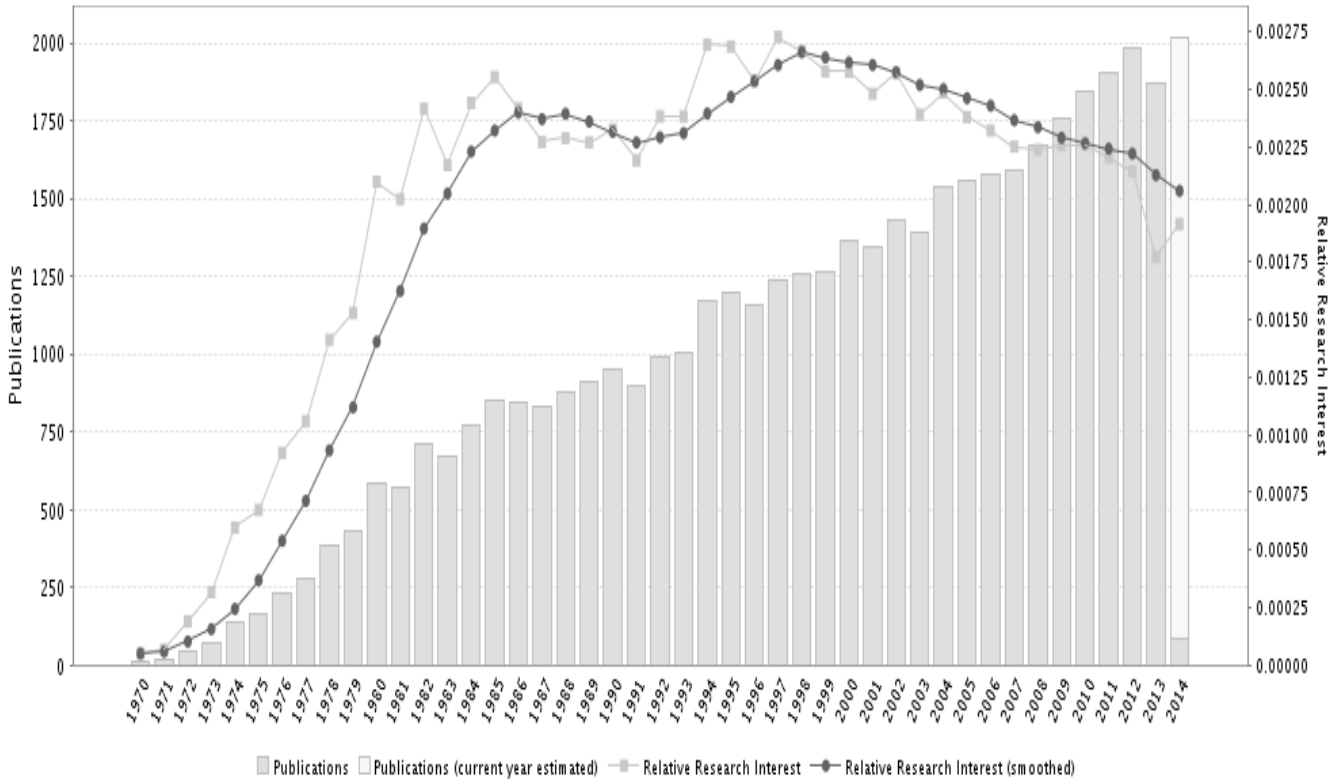

Figure-3(a)
Survey results for liposomes alone

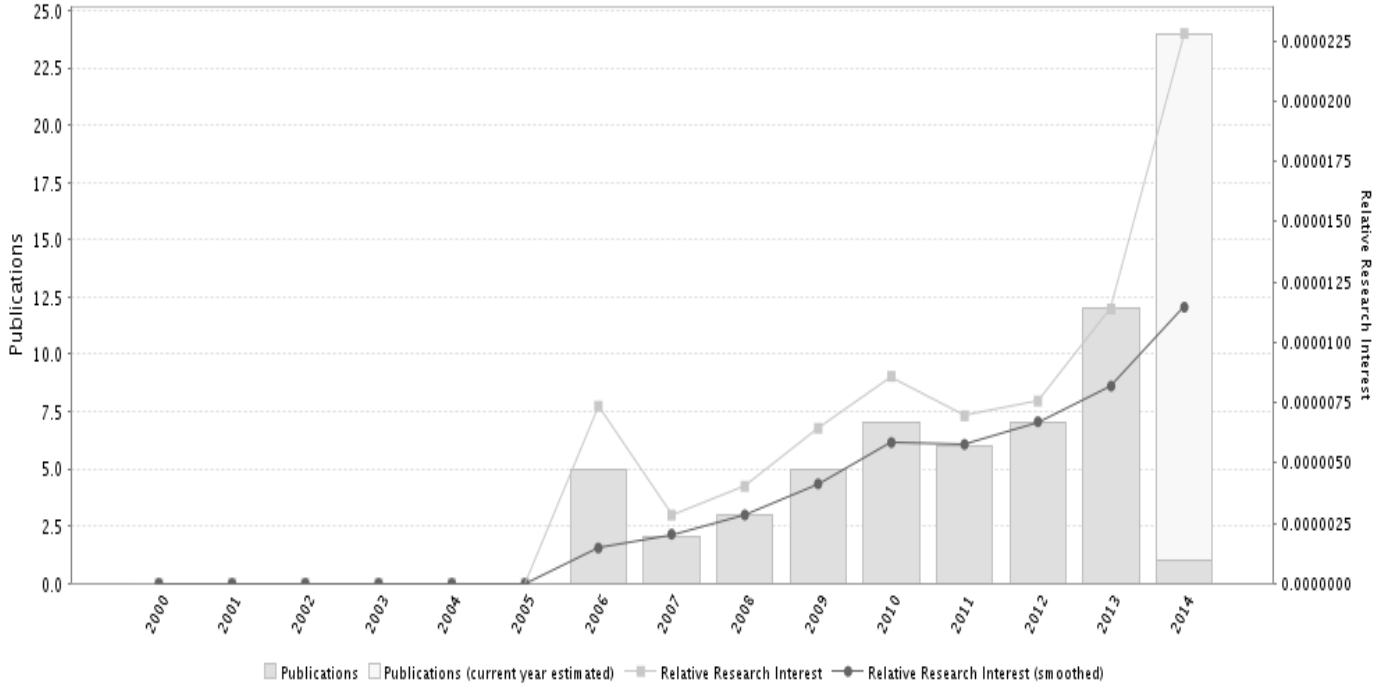

Figure-3(b)
The survey results of nano-liposomes
The comparison clearly shows that with the merger of the two technologies there is a very steep rise showing the rising interest in this novel emerging technology

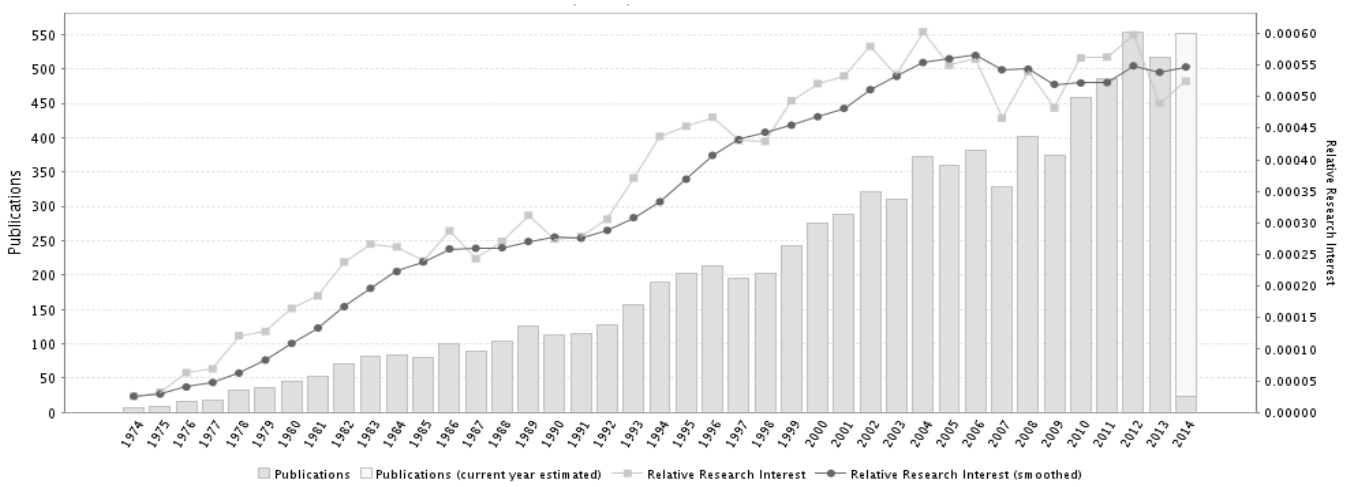

Figure-4(a)
The survey results on liposomes

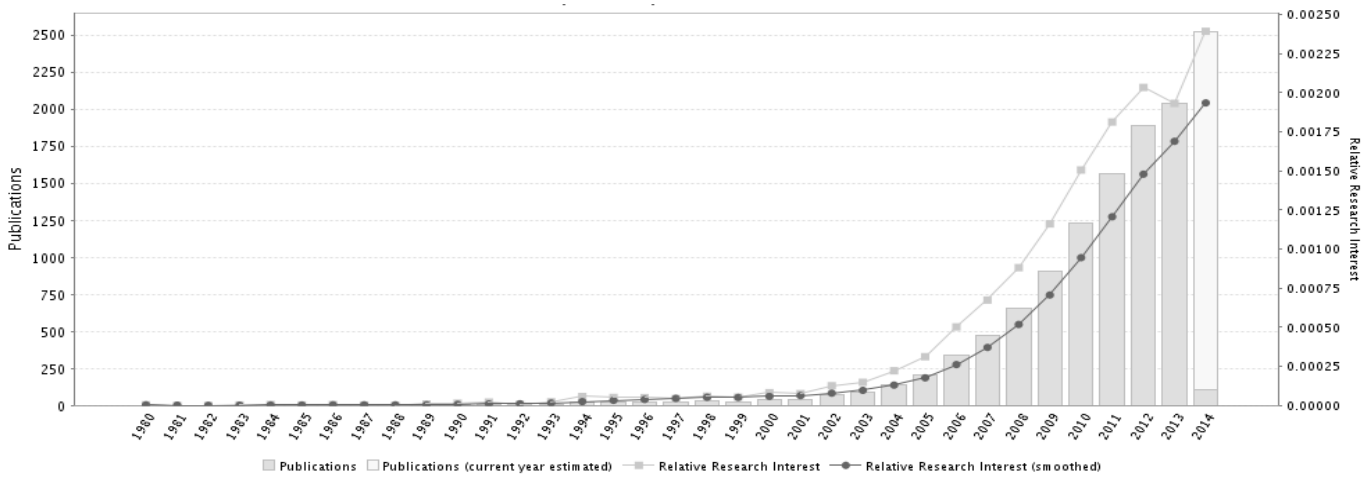

Figure-4(b)
nanoparticles shows its large application in cancer therapeutics

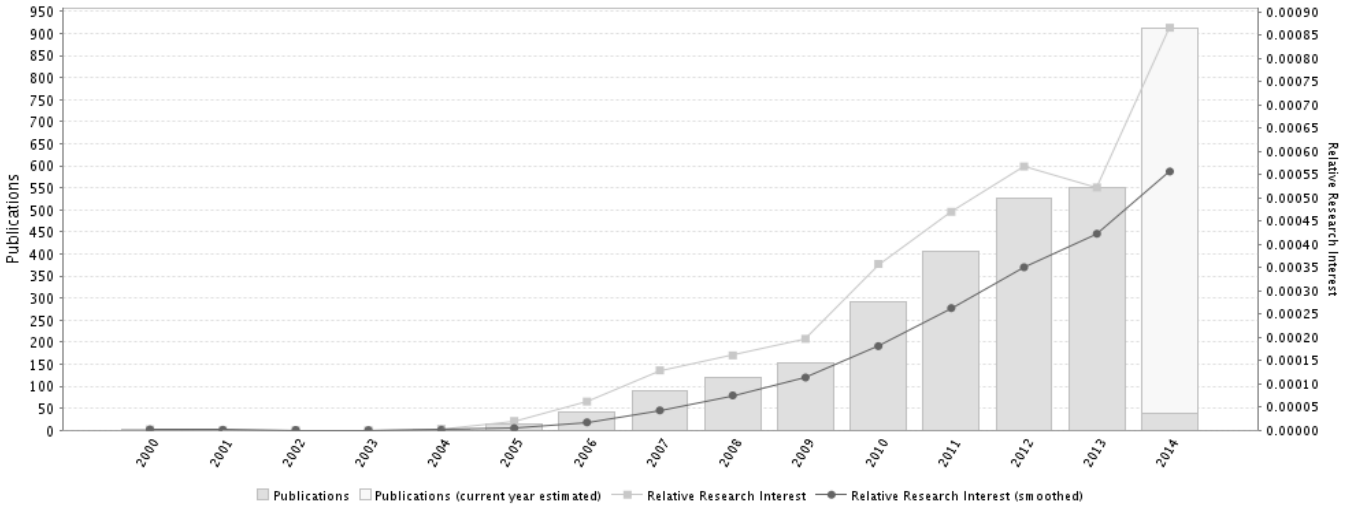

Figure-4(c)
An overall hike proportional to rising interests of research community is shown by results

Publication survey for research popularity: The publication survey is divided into three parts and each division focussed the subject popularity, research interests and publications map accessed for various key terms. Firstly nanotechnology and nanomedicine are studied alone. This really does not correspond to a good show as can be seen in Figure 2. The reason can be the existence of more multidisciplinary streams to study the complexity of life. Then same parameters are considered individually for liposomes and nano-liposomes. Figure 3(a) illustrates the survey results for liposomes alone and figure 3(b) shows the survey results of nano-liposomes. The comparison clearly shows that with the merger of the two technologies there is a very steep rise that corresponds to the rising interest in this novel emerging technology. Figure 4 corresponds to the most interesting facts. In these liposomes, nanoparticles are studied for its potential applications in vivid cancer therapies. Despite of the fact that liposomes alone have gained great popularity in cancer treatment the interest and research focus in nanoparticles is also seen rising steeply. This figure also shows its large application in cancer therapeutics and an overall hike proportional to rising interests of research community is shown by results. These results provide an explanation to the timeline of emergence of liposomes and nanoparticles.

Conclusion

Biosciences along with informatics disciplines presently envelop a spacious scientific and technological progress. All these efforts lead to resolve multifaceted problems dealing with data and knowledge assimilation majorly pertaining to biomedical terminology, data mining proficiency, genome sequencing techniques, medical networking, predicting interactions among biomarkers, gene alterations, diseases and their treatments, drug delivery vehicles, improvement in methodology, tools focused to deal with simulation studies, data-integration and data-retrieval related to various biological systems.

The main motto of medication is accurate and early diagnosis of a unhealthy condition and provide a effective treatment while avoiding potential side-effects. Nanotechnology provided a new direction to fulfil this motto with aid of informatics. Nano-materials have gained popularity in medical applications as novel diagnostic tools, drugs and drug carriers. Several liposomes have also been discovered and registered with a successful story in pharma-market. For illustration purpose FDA study is also summed up in table-1[39].

Table-1
FDA approved nano-medicines

Drug name	Composition/active ingredient	Dosage form/route	Original or tentative approval date	indication	Review classification
Abelect	Amphotericin B	Injectable, Lipid Complex; Injection	November 20, 1995	Invasive fungal infections	-
Camptosar	Irinotecan Hydrochloride	Injectable; Injection	June 14, 1996	-	Priority review drug
Doxil (Liposomal)	Doxorubicin Hydrochloride	Injectable, Liposomal; Injection	November 17, 1995	Various cancers	Orphan drug
Orencia	Abatacept	Injectable; IV (Infusion)	December 23, 2005		-
Ambisome	Amphotericin B	Injectable, Liposomal; Injection	August 11, 1997	Fungal and protozoal infections	-
Cimzia	Certolizumab Pegol	Injectable; Injection	April 22, 2008	-	-
Binosto	Alendronate Sodium	Tablet, Effervescent; Oral	March 12, 2012	-	Standard review drug
Macugen	Pegaptanib Sodium	Injectable; Intravitreal	December 17, 2004	-	Priority review drug
Arestin	Minocycline Hydrochloride	Powder, Extended Release; Dental	February 16, 2001	-	Standard review drug

Source FDA, accessed 15 may 2014

The time is seeing a promising future for both nano and liposomal technologies to deal with the growing sophisticated neurological and cancer therapies. In near future nano-sized liposomes will revolutionize the drug delivery systems especially for cancer therapies that deal with drug delivery across blood brain barriers.

References

1. Dan Peer, Jeffrey M. Karp, Seungpyo Hong, Omid C. Farokhzad, Rimona Margalit and Robert Langer, Nanocarriers as an emerging platform for cancer therapy, *nature Nanotechnology,* **2,** 751-760**(2007)**

2. Phan J.H., Moffitt R.A., Stokes T.H., Liu J., Young A.N., Nie S. and Wang M.D., Convergence of biomarkers, bioinformatics and nanotechnology for individualized cancer treatment, *Trends Biotechnol,* **27(6)** 350-358 **(2009)**

3. Maojo V. et al, Nanoinformatics: developing new computing applications for nanomedicine, *Computing,* **94(6)** 521-539 **(2012)**

4. Jesus M. de la Fuente V. Grazu, Nanobiotechnology Inorganic Nanoparticles vs Organic Nanoparticles, *Frontiers of Nanoscience,* **(2012),** ISBN: 0124157696)

5. Ambrogi F., Coradini D., Bassani N., Boracchi P. and Biganzoli E., Bioinformatics and Nanotechnologies: Nanomedicine. In: Kasabov N, ed., *Springer Handbook of Bio-/Neuroinformatics*: Springer Berlin Heidelberg, 517-532 **(2014)**

6. Sheng W.Y. and Huang L., Cancer immunotherapy and nanomedicine, *Pharm Res.,* **28(2)** 200-214 **(2011)**

7. Ranjan Sanjeev, Liposome Nanoparticles for Targeted Drug Delivery, Gene Delivery and Magnetic Imaging, 137 **(2012)**

8. Slingerland M., Guchelaar H.J. and Gelderblom H., Liposomal drug formulations in cancer therapy: 15 years along the road, *Drug Discov Today,* **17(3-4)** 160-166 **(2012)**

9. Pinheiro M., Lúcio M., José L.F.C. Lima, Salette Reis, Liposomes as Drug Delivery Systems for the Treatment of TB, *Nanomedicine.,* **6(8)** 1413-1428 **(2011)**

10. Gulati M., Bajad S., Singh S., Ferdous A.J. and Singh M., Development of liposomal amphotericin B formulation, *J Microencapsul.* **15(2)** 137-151 **(1998)**

11. Sanvicens Nuria and Pilar Marco M., Multifunctional nanoparticles – properties and prospects for their use in human medicine, *Trends in Biotechnology,* **26(8)** 425-433 **(2008)**

12. Yezhelyev M.V. et al. Emerging use of nanoparticles in diagnosis and treatment of breast cancer, *Lancet Oncol,* **7,** 657–667 **(2006)**

13. Pison U. et al. Nanomedicine for respiratory diseases, *Eur. J. Pharmacol,* **533,** 341–350 **(2006)**

14. Ramishetti S. and Huang L., Intelligent design of multifunctional lipid-coated nanoparticle platforms for cancer therapy, *Ther Deliv.,* **3(12)** 1429-1445 **(2012)**

15. Zhang Y., Peng L., Mumper R.J. and Huang L., Combinational delivery of c-mycsiRNA and nucleoside analogs in a single, synthetic nanocarrier for targeted cancer therapy, *Biomaterials,* **34(33)** 8459-8468 **(2013)**

16. Alyautdin R., Khalin I., Nafeeza M.I., Haron M.H. and Kuznetsov D., Nanoscale drug delivery systems and the blood-brain barrier, *Int J Nanomedicine,* **9,** 795-811 **(2014)**

17. Ribatti D., Nico B., Crivellato E. and Artico M., Development of the blood–brain barrier: a historical point of view, *Anat Rec B New Anat.*, **289(1),** 3–8 **(2006)**

18. Lewandowsky M. Zur Lehre von der Cerebrospinal flüssigkeit, On the cerebrospinal fluid, X Z Klin *Med*., **40,** 480–494 **(1900)**

19. Begley D.J., Delivery of therapeutic agents to the central nervous system: the problems and the possibilities, *Pharmacol Ther.*, **104,** 29–45 **(2004)**

20. Begley D.J., The blood–brain barrier: principles for targeting peptides and drugs to the central nervous system, *J Pharm Pharmacol.*, **4,** 136–146 **(1996)**

21. Bernacki J., Dobrowolska A., Nierwińska K. and Malecki A., Physiology and pharmacological role of the blood–brain barrier, *Pharmacol Rep.*, **60,** 600–622**, (2008)**

22. Abbott N.J., Dynamics of CNS barriers: evolution, differentiation and modulation, *Cell Mol Neurobiol*., **25,** 5–22 **(2005)**

23. Abbott N.J., Comparative physiology of the blood–brain barrier. In: Bradbury, MWB, editor. Physiology and Pharmacology of the Blood–Brain Barrier, *Heidelberg: Springer-Verlag,* 371–396 **(1992)**

24. William M. Pardridge, Drug Delivery Across the Blood-Brain Barrier, *Journal of Cerebral Blood Flow and Metabolism,* **32,** 1959–1972 **(2012)**

25. Pardridge W.M., Blood-brain barrier delivery, *Drug Discov Today,* **12,** 54-61 **(2007)**

26. Pangalos M.N., Schechter L.E. and Hurko O., Drug development for CNS disorders: strategies for balancing risk and reducing attrition, *Nat Rev Drug Discov,* **6(7)** 521-532 **(2007)**

27. Samad A., Sultana Y. and Aqil M., Liposomal drug delivery systems: an update review, *Curr Drug Deliv,* **4(4),** 297-305 **(2007)**

28. Srinivas Ramishetti, Leaf Huang, Intelligent design of multifunctional lipid-coated nanoparticle platforms for cancer therapy, *Ther Deliv*., **3(12),** 1429–1445 **(2012)**

29. Dominguez A., Suarez-Merino B. and Goni-de-Cerio F., Nanoparticles and blood-brain barrier: the key to central nervous system diseases, *J Nanosci Nanotechnol,* **14(1),** 766-779 **(2014)**

30. Kaiser J.M., et al., Nanoliposomal minocycline for ocular drug delivery, *Nanomedicine: NBM*, **9,** 130-140 **(2013)**

31. Ko A.H., Tempero M.A., Shan Y.S., Su W.C., Lin Y.L., Dito E., Ong A., Wang Y.W., Yeh C.G. and Chen L.T., A multinational phase 2 study of nanoliposomal irinotecansucrosofate (PEP02, MM-398) for patients with gemcitabine-refractory metastatic pancreatic cancer, *Br J Cancer,* **109(4),** 920-925 **(2013)**

32. Hosny K.M., Ahmed O.A. and Al-Abdali R.T., Enteric-coated alendronate sodium nanoliposomes: a novel formula to overcome barriers for the treatment of osteoporosis, *Expert Opin Drug Deliv,* **10(6),** 741-746 **(2013)**

33. Liang J., Wu W., Liu Q. and Chen S., Long-circulating nanoliposomes (LCNs) sustained delivery of baicalein (BAI) with desired oral bioavailability in vivo, *Drug Deliv.* **20(8),** 319-323 **(2013)**

34. Subramanian M., Holopainen J.M., Paukku T., Eriksson O., Huhtaniemi I. and Kinnunen P.K., Characterisation of three novel cationic lipids as liposomal complexes with DNA, *Biochim BiophysActa.* **1466(1-2),** 289-305 **(2000)**

35. Saily V.M., Ryhanen S.J., Lankinen H., Luciani P., Mancini G., Parry M.J. and Kinnunen P.K., Impact of reductive cleavage of an intramolecular disulfide bond containing cationic gemini surfactant in monolayers and bilayers, *Langmuir,* **22(3),** 956-962 **(2006)**

36. Ryhanen S.J., Saily M.J., Paukku T., Borocci S., Mancini G., Holopainen J.M. and Kinnunen P.K., Surface charge density determines the efficiency of cationic gemini surfactant based lipofection, *Biophys J.,* **84(1),** 578-587 **(2003)**

37. Doms A. and Schroeder M., GoPubMed: exploring PubMed with the Gene Ontology, *Nucleic Acids Res.,* **33, Web Server issue,** W783-786 **(2005)**

38. Sinha R., Kim G.J., Nie S., Shin D.M., Nanotechnology in cancer therapeutics: bioconjugated nanoparticles for drug delivery, *Mol Cancer Ther.,* **5(8),** 1909-1917 **(2006)**

39. Jabr-Milane L.S., van Vlerken L.E., Yadav S. and Amiji M.M., Multi-functional nanocarriers to overcome tumor drug resistance, *Cancer Treat Rev.,* **34(7),** 592-602**, (2008)**

40. FDA Food and Drug Administration (http://www.fda.gov /Drugs/default.htm) (http://www.accessdata.fda.gov/Scripts /cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug _Name) last Accessed on 15 may 2014 **(2014)**