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Cancer Bioinformatics in Cancer Therapy

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Abstract

Last three decades, this world witnesses a rapid progress of biomarkers and bioinformatics in a lot of biomedical study. Cancer bioinformatics is one of such important omics areas. Same as other biological techniques, bioinformatics are presently not Omni-potent. Despite technical advances, cancer bioinformatics has its own limitations at this stage. This article will overview bioinformatics in cancer study and clinical applications—advantages and limitations associated with cancer therapeutics and drug developments. Finally, creative ideas and future perspectives are highlighted.

Keywords: Cancer Bioinformatics; Cancer Stem Cells; Cancer Therapy; Drug Developments; Neoplasm Metastasis; Personalized Cancer Therapy

Introduction

Background

Cancer remains to be a serious human health problem that claims life about 7-10 million people annually in the world. During last 30 years, this world witnesses a rapid progress of bioinformatics study and wide-range of clinical applications worldwide. Since cancer bioinformatics diagnostic systems have advantages and shortcomings, their popularity in cancer practices need to promote worldwide. Many obstacles need to be overcome. The object of this study is to promote cancer bioinformatics diagnostic strategy in clinical cancer trials. This article not only offers a panorama of bioinformatics in cancer researches and wide-range of clinical applications, but also highlights possible improvements in the future.

A Role in Cancer Diagnosis and Drug Response Predictions

Cancer is a progressive disease and genetic and molecular abnormalities are growing in an enlarged tumor tissues [1,2]. The best therapeutics in the clinic should be designed according to this changeable state. Nonetheless, different types of cancer genesis are caused by different genetic alterations, such as mutation, translocation, deletion, replication and metabolisms [3,4]. Bioinformatics diagnosis is useful for therapeutic prediction by revealing this ever-change cancer malignant state. Certainly, many categories of personalized cancer therapies are widely utilized globally [5-9]. In this article, the scenarios of cancer bioinformatics studies and clinical applications are introduced.

Technical Analysis

Oncologic Identification (Bioinformatics Hallmarks) In Different Cancer Categories

Cancer is a different disease with an identical pathological property of unlimited growth, invasion and metastasis in distant tissues. Overall, it is classified unto six hallmarks-(Table 1) [4]. Different cancer hallmarks can be observed by different bioinformatics and predicted to different anticancer drug responses and choices.

Hallmarks of cancer	Possible molecular or pathological mechanisms
Sustaining proliferative signaling	Somatic mutation, unlimited proliferative, signal overdone, environmental stress
Resisting cell death	Apoptosis (caspases, Bcl-2, Bax etc) and autophagy
Inducing angiogenesis	Vascular, inflammatory factors (VEGF, TNF) and so on
Evading growth suppressors	Tumor growth suppressors (RB, TP53) etc

Enabling replicative immortality	Telomerase
Invasion and metastasis	Different pathologic stages and molecular changes

Table 1: Biology and pathology mechanisms of cancer.

From Biomarkers to Bioinformatics

Cancer biomarker detections are pioneered with several tumor pathogenic molecules (commonly protein or glycol-protein, such as α–feto proteins or CEA). Hospitals diagnose these molecules (biomarkers) one by one. Targeted monoclonal antibodies or other targeted anticancer drugs are proposed to exhibit higher therapeutic efficacies against escalated cancer biomarkers and tumor growth in patients.

Cancer bioinformatics methods are relatively high throughput (generally > 10 biomolecules by modern chromatography; >5000 genetic allele polymorphisms by micro-arrays including tumorigenic initiators, promoters, somatic mutations, transcriptions by reversed-RNA sequencing with PCR-related techniques and so on [10-18].

Since tumors are progressive and chronic diseases with more than a hundred genetic changes of a single cell in advanced cancer patients [6], high-throughput methodology is needed to identify ever-changing underlying cancer abnormalities in cells (plasticity) [19-21]. The multidisciplinary nature of bioinformatics makes them relatively easier for pathological grading and therapeutic response prediction. Thanks to the fast-pace of bioinformatics technical evolutions and the assistance of mathematical or computational network [9-18], cancer bioinformatics determinations and analyses need lower and lower running-costs [22-24]. Individualized treatment based on detecting genetic or molecular variations by different modern strategies is growing popularity. High throughput bioinformatics detecting may help to transform clinical diagnosis from several molecules into several hundred molecule-based strategies in the future. It relies on balance between clinical benefits and economic considerations (hospital conditions) if possible [23,24].

Since the heterogeneity of cancer origin and genesis factors is increased with disease progresses and cancer metastasis, it suggests that some hidden rules behind scenes are not established (Figure 1). Currently, we are too naïve to believe that tumor bioinformatics can be understood all tumor biological information by detecting only one tumor biopsy or surgery samples. How to optimize diagnostic or drug predictive strategies is still a mystery. Thence, the hidden rule discoveries by bioinformatics translation into therapeutic paradigms are inevitable future studies and trends.

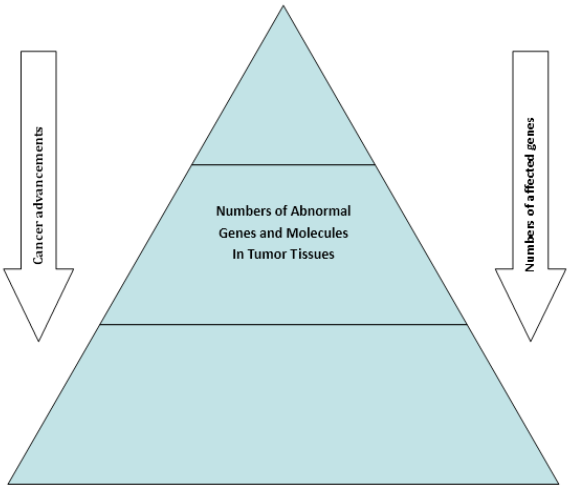

Figure 1: A picture of cancer genetic/molecular progressions in each solid tumor advancement.

Cancer Genomes

Cancers commonly originate through a variety of genetic dysfunction unto molecular malformation. Knowing the cancer genome can help us to understand the origin and advancements of cancers cells and/or variable response of pharmacotherapy [5-9, 25]. Yet, this medical cliché needs to be customized in the clinic. Approximately more than one thousand types of genetic abnormality can be found in advancing tumors within human bodies. To judge with this great change of cancer genome and more than 100 anticancer drugs worldwide, understanding patho-therapeutic relationships before formal cancer medications in the clinic is required. Even with a certain amount of tumor type, such as lung cancer, ovarian or mammary cancer, the responses to the same anticancer drugs may vary from patient to patient.

Bioinformatics, a genomics-supportive approach that provide a variety of technical capabilities can analyze DNA, RNA, proteins, glycoligands and metabolisms for single level or as a whole in cancer patients.

In the earliest era, biomarkers or bioinformatics evaluation was to meet the requirement of patients' prognoses [10] or classify tumor origins [11] in the clinic. More recently, the advancing utility of cancer biomarkers or bioinformatics in predicting anticancer drug responses is validated.

Getting Popularity in The Clinic

Finding the bioinformatics changes in cancer tissues is only the first step in clinical cancer trials; the choice of effective targeted

anticancer drugs for individual cancer patients is the new challenge in the clinical trials [5-9]. The detection of cancer bioinformatics without therapeutic response prediction is meaningless and waste of time and money. Thence, bioinformatics-therapeutic relation must be built. Validity of the cancer biomarkers or bioinformatics that drug response is general topic for bioinformatics applications. To achieve this goal, effectively targeted anticancer drugs are needed [26-29]. If we do not equip with useful drugs, we cannot properly control cancer growths and metastasis no matter how crystal clear we know oncologic features by cancer bioinformatics. Development and approval of more effective targeted anticancer drugs are indispensable for personalized cancer medicine [26-29].

Key for Biomarker to Bioinformatics

Discovery of Original Causes of Tumors

In the very beginning of oncologic-based therapy prediction studies and applications, only one or two biomarkers (such as fetoprotein) are observed in the clinic. It is, nonetheless, too little and too limited scale due to the complex of tumor genesis, invasive-metastatic cascade and therapeutics [30-37]. Overall mutant genetic alleles or molecular abnormalities are huge when patients want to treat cancer. Since human and onco- genomes are more than a bundle of genes, simultaneous detection of genomics, proteomics, glycoprotein changes and metabolomics among individual cancer patients are necessary and indispensable. Detections of proteins or glycoproteins are relatively straightforward than human genome diagnosis from therapeutic predictive basis. Oncogenomic information must extrapolate complicated information for therapeutically predictive purpose [30-37]. Human or oncogenomic contain non-coding RNA genes, regulatory sequences, structural motifs; it maintains short-range and long-range spatial organization and translocations of sequences; also, it contains evolutionary information [3,4]. Thus, extrapolation of tumor genomic abnormalities needs high-end technologies, revolutionary biological knowledge and workable calculating systems. The more knowledge we learn from the human genome, the more useful genetics-guided therapeutic paradigms can be chosen from and optimal clinical outcome can be predicted.

Identifying and validating the originally causal biomarkers from wealth malignancy and metastatic molecules for individualized chemotherapy is a top priority and pharmacological significances [5-9]. It includes mathematical or computational systems to decipher genomic or molecular mutants into improved therapeutic interventions [38-42]. To attain this goal, expanding basic and clinical investigations are needed to establish paradigms of universal utility. These clinical paradigms ought to be easy to handle, economic, high-throughput, and predictable. It is recommended that an international committee should be built to meet with all technical requirement of standard micro-chips or hospital routines in order to safeguard the clinical diagnostic/therapeutic quality (survival benefits) and economical for patient's choice [43].

Mathematical Modality and Computational Network

Reduce the Complexity of Biological Study

The complex interaction and interplay between molecular-to-molecular and tumor-normal cells can been fully discovered by biomedical techniques alone. Increasing complexity of genes and molecules can be gradually monitored or analyzed by mathematic or computational network. (Figure 1) shows that great number of mutant genes or molecules is increased along with tumor progresses and neoplasm metastasis. The mathematical treatments of cancer bioinformatics data can help some cancer therapists who have little knowledge of cutting-edge biomedical technology to perform cancer therapeutic efficacy predictions in the clinic.

Advantage of Mathematical Work

Advantage of mathematics in bioinformatics data analysis is obvious and straightforward-pervasive in various fields of biology and medicine [38-42]. Without high-quality mathematics or computational network, doctors will be overwhelmed by wealth of bioinformatics data and do nothing for therapeutic prediction. Mathematical modeling and computational networks are powerful tools for identification of mutated genetic alleles and therapeutic decision-making. These tools help us to identify crucial drug targets, weigh and balance each variable among overall genetic/molecular background in tumor tissues and finally coordinate matched drugs to inhibit or kill tumor cells. In general, since mathematical treatment is an effective means for integrating and coordinating multi-variant data between diagnosis/therapies. This is why mathematical approaches and computational network become growing importance in the fields of ICT in the clinic.

Biological Rule and Mathematical Participation

Mathematics data analysis in the field of bioinformatics-based cancer personalized therapies is more than an issue of algebra, exponential or iterative. Understanding of the interplay between diverse cancer genes and pathologic bio-molecules is indispensable. Undiscovered biological rules might also participate. These interplays are not mathematics only, but biological as well. For example, cross-talks between different cell signals are rationale approaches are not easily calculated by regular mathematical systems and network. Furthermore, tumor environmental matrix, metastatic-mediated pathways and cancer stem change also decide tumor progressions and malignancy. Future mathematic capability ought to be more sophisticated than ever before. Moreover, tumor promoters and suppressors are opposite factors for tumor progresses and metastasis. They are sometimes algebra, sometimes exponential and sometimes biology. It depends on the characteristics of different clinical condition. Currently, biological information treatment via mathematical models is often outside our reaches (general oncologists and clinicians). This kind of golden rush is waiting our great explorations. Working together among mathematicians, biologists and therapists is a future topic of cancer genetic or bioinformatics studies-including many types

of systems biology or medicines by teamwork.

Association Between Oncology and Pharmacology System

Overview

Association and difference between oncologic data (tomography, metastatic stage, genomics and bioinformatics) and pharmacology (drug activity and sensitivity, drug combination choice) for therapeutic prediction in individual cancer patients is obvious. (Figure 2) Looking at different categories of cancer therapeutic strategies are supported by different technologies. Due to the limitation of patho-therapeutic relation knowledge, one strategy of ICT cannot meet all requirements of maximum therapeutic match. It is quite interesting if one technology can provide detail information of both biomedical disciplines (oncology as well as pharmacology) [44-45].

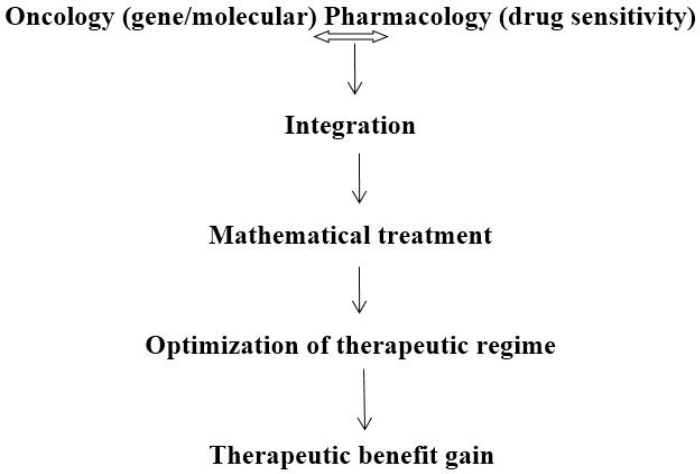

Figure 2: Outlook of modern personalized medicine.

Cancer Pathology and Bioinformatics

It is recently known that approximately 30,000 genes consist in normal and cancer human cells. Each cancer cell has distinctive and unique set of genetic makeup (up- or down-regulated in a tumor masses than normal cells from these ~30,000 genes) [32]. Only one or two genes are likely to be the original genetic abnormalities for cancer patients. When the genetic status of a tumor is assessed, only an average or overall picture of gene expression is observed. Bioinformatics (genomics, proteomics and metabolomics in cancer cells) reveals larger biological information in individual cancer patients.

Usually, only a few cancer biomarkers are detected in routine diagnostic procedures in general hospitals. The origin of a tumor is unlikely to be fully identified by this hospital routine and drug predictions. More comprehensive approaches for mapping the genetic polymorphisms, biochemical analysis and cytological levels of cancer-associated biomarkers versus increasingly sophisticated mathematical means will meet the requirements of real culprit catch-up. More computer software that supports automatic prediction of drug responses and toxicities (like artificial intelligence AI system) might be developed and especially recommended to future hospitals.

Emerging Topics for Cancer Bioinformatics

Therapies Against Neoplasm Metastasis and Cancer Stem Cells

Cancer metastasis is the key factor for cancer patients' deaths (>90 cancer mortality in the clinic) [46-52]. Currently, cancer pharmacotherapy mainly focuses on primary tumors rather than neoplasm metastasis and antimetastatic drugs are not widely developed [46-54]. Moreover, many ICT methods, such as Drug Sensitivity Tests (DST) [55-57] or Pharmacogenomics (PG) [58] are also designed to primary tumors in the clinic. So cancer patients' survival has been improved in a small extent. Antimetastatic drug developments and studies are not fruitful owing to above-mentioned reasons. Developments of more effective antimetastatic drugs, especially against formed metastatic foci, neoplasm metastasis treatments according to clinical circumstance of patients must be emphasized [50,52]. Some possibilities of assistant therapies by developing more effective, low toxicity supporting drugs and clinical optimizing therapeutic regimes can lead to breakthrough and next-generations of cancer therapies. The state-at-the art systems of cancer bioinformatics studies

Cancer stem cells in tumor tissues commonly decide therapeutic outcomes in the clinic. The cancer stem cells often renew themselves in cancer tissues that processes are hardly manageable by present treatment conventions (drugs and others) [59-62]. These self-renewals of cancer cells increase tumor malignancy in many pathogenesis aspects (dedifferentiation, dormancy, invasion, metastasis, relapse, chemotherapy-refractory, immune-escape and stimulating angiogenesis of tumors) [59-63]. Thus cancer bioinformatics are suitable for revealing ratio and biology of cancer stem cells in the future. Yet, cancer stem cells are less than 10 % in primary or formed metastatic tissues [64], it is still difficult to observe status of cancer stem cells in tumor tissues by present bioinformatics techniques and procedures. Future creative ideas and techniques are desperately needed.

Drug Combinations and Cancer Bioinformatics

Since most cancers have diverse genetic alterations and molecular abnormalities, cancer therapeutics is seldom very useful by only one anticancer drug. It has been widely accepted that anticancer drug cocktail instead single drugs might promote the control of cancer progresses and metastasis in clinical trials [65-68]. Similarly, are other chronic diseases, such as HIV/AIDS [69] and type 2 diabetes [70-71]. Most importantly, anticancer drug cocktails need to transform from empirical to science-guided enterprises [67-68]. Cancer bioinformatics is one of such avenue for identifying and choice of anticancer drug combination. Only through this strategy, cancer therapy can make a difference.

Future Perspective

Technical Innovation and Selections

Currently, bioinformatics is diverse in standard techniques and need to be uniformed by manufacturers [6]. In order to safeguard the quality and cost of hospital routines, standard guidelines must be issued internationally every 4-5 years.

Validity of cancer biomarkers or bioinformatics from tumor samples and prediction of anticancer drugs or biotherapies are general schemes for cancer bioinformatics applications. To achieve this goal, effectively drug choices (pharmacology) and clinical genetic/molecular predictions (oncology) must be integrated in the clinic [72-76]. Building central dogma for cancer bioinformatics analysis and drug response predictions is an unavoidable pathway in clinical rationales in the future [77-78].

Four categories of clinical investigations might be useful for cancer biomarker/bioinformatics-based cancer therapies:

- Improve the capacity of identification and validity for system updating of cancer biomarkers or bioinformatics for therapeutic purposes;
- Technical updating for economic considerations-put into large-scale production;
- Balancing between drug responses and toxicities from varying genetic abnormalities; and finally;
- Modern diagnostic systems in the real-time and non-invasive situations in cancer patients [2].

Cost-Reduction and Clinical Optimizing

Personalized cancer therapy (PCT) from detecting cancer biomarkers or bioinformatics is a modern strategy and has a great therapeutic potential in the clinic. However, the cost of cancer biomarker detection (generally $100-5000) is relatively low and cost-effective than other items of cancer treatments. It is especially cost-effective for early stages or young cancer patients owing to high rates of therapeutic survival benefits [15,43].

With the advancement of bioinformatics techniques, ICT with cancer biomarkers/bioinformatics detection will have a great impact in the future [77,78]. It is one of the fastest growing fields of PCT in future. But many important issues for cancer bioinformatics applications are unresolved. Economic consideration and cost-reduction for bioinformatics diagnostics can provide good service for more cancer patients and technical providers. Any unilateral economic benefits will not a healthy one. Finding leverage of these medical services is the key.

Advancing Knowledge

Earliest phase of cancer bioinformatics-based hypothesis and therapeutic studies are come from intuitions. Up to now, there is no good relationship (linear or multi-level) between abnormal cancer biomarker ranges and therapeutic outcomes (especially survival benefits) in clinical trials. Past medical evidence showed that no solid relationship between drug responses and scale or levels of most tumorigenic escalation can be based. To this obvious drawback, advancing knowledge of neoplasm/metastasis/mechanisms of action of anticancer drugs must be investigated in a large-scale. Why and how these clinical manifestations become a reality have yet to be defined. The elevated cancer biomarkers or bioinformatics characters are only parts of molecular basis in tumor growth and metastasis. Thus, breakthroughs within or beyond the bioinformatics techniques may all helpful for the promotion of clinical cancer trials.

Conclusion

Currently, less than 10% of patients use cancer-bioinformatics-based PCT-far behind PG and DST. The techniques and supporting systems in cancer bioinformatics are however developing rapidly-including new idea generations and novel models/drug developments. Cancer bioinformatics is still in its infancy. No decisive role has been played in clinical cancer treatments via this spectrum of techniques. Next generation of PCT strategies (integration of oncology and pharmacology) will play leading role in the future [77-78].

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Competing Interests

Authors have declared that no competing interests exist

References

1. Lu DY, Lu TR, Chen XL, Chen EH, Ding J, et al. (2015) Cancer bioinformatics, its impacts on cancer therapy. Metabolomics 5: 133.
2. Lu DY, Qi RX, Lu TR, Wu HY (2017) Cancer bioinformatics for updating anticancer drug developments and personalized therapeutics. Reviews on Recent Clinical Trials 12: 101-110.
3. Nowell PC (1976) The clonal evolution of tumor cell populations. Science (Washington DC), 194: 23-28.
4. Hanahan D, Weinberg RA (2011) Hallmarks of cancer, the next generation. Cell 144: 646-674.
5. Lu DY, Chen XL, Ding J (2006) Individualized cancer chemotherapy integrating drug sensitivity tests, pathological profile analysis and computational coordination-an effective strategy to improve clinical treatment. Med Hypotheses 66: 45-51.
6. Lu DY, Lu TR, Chen XL, Ding J (2012) Individualized cancer chemotherapy. Hypotheses in Clinical Medicine. Ed, Shoja MM, Agutter PS, Tubbs RS, Ghanei M, Ghabili K, Harris A, Loukas M. chapter 13, 199-216 Nova Science Publisher US 2012.
7. Lu DY, Lu TR, Wu HY (2014) Personalized cancer therapy, a perspective. Clinical Experimental Pharmacology 4: 153.
8. Lu DY, Lu TR, Che JY, Wu HY (2014) Individualized cancer therapy. Innovations in Pharmaceuticals and Pharmacotherapy 2: 458-469.

9. Lu DY (2014) Personalized cancer chemotherapy, an effective way for enhancing outcomes in clinics. Woodhead Publishing, Elsevier, UK 2014.

10. Van de Vijver MJ, He YD, van't Veer LJ, Dai H, et al. (2002) A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 347: 1999-2009.

11. Gordon GJ, Jensen RV, Hsiao LL, Gullans SR, Blumenstock JE, et al. (2002) Translation of microarray data into clinically relevant cancer diagnostic tests using gene expression ratios in lung cancer and mesothelioma. Cancer Res 62: 4963-4967.

12. Olson BM, McNeel DG (2013) Monitoring regulatory immune responses in tumor immunotherapy clinical trials. Frontier in Oncology 3: 109.

13. Dalton WS, Friend ASH (2006) Cancer biomarkers-an invitation to the table. Science 312: 1165-1168.

14. Ocana, A, Pandiella (2010) A Personalized therapies in the cancer "omics" era. Mol Cancer 9: 202.

15. Retel VP, Joore MA, Knauer M, Linn SC, Hauptmann M, et al. (2010) Cost-effectiveness of the 70-gene signature versus St. Gallen guidelines and Adjuvant Online for early breast cancer. European Journal of Cancer 46: 1382-1391.

16. Stransky B, Galante P (2010) Application of bioinformatics in cancer research. An IMICS Perspective on Cancer Research 211-233.

17. Strausberg RL, Simpson AG, Old LJ, Riggins GL (2004) Oncogenomics and the development of new cancer therapies. Nature 429: 469-474.

18. Lu DY, Lu TR, Cao S (2012) Individualized cancer chemotherapy by detecting cancer biomarkers. Metabolomics 2: 121.

19. Nieto MA, Huang RY, Jackson RA, Thiery JP (2016) EMT: Cell 166: 21-45.

20. Lu DY, Lu TR, Xu B, Qi RX, Sastry NY, et al. (2016) Cancer metastasis, a clinical dilemma for therapeutics. Current Drug Therapy 11: 163-169.

21. Lambert AW, Pattabiraman DR, Weinberg RA (2017) Emerging biological principles of metastasis. Cell 168: 670-691.

22. Marx V (2013) Tracking metastasis and tracking cancer. Nature 494: 131-136.

23. Jongeneel CV, Iseli C, Stevenson BJ, Riggins GJ, Lal A, et al. (2003) Comprehensive sampling of gene expression in human cell lines with massively parallel signature sequencing. Proc Natl Acad Sci 100: 4702-4705.

24. Lu DY, Lu TR, Wu HY (2013) Cost-effectiveness considerations of individualized cancer chemotherapy. Advances in Pharmacoepidemiology & Drug Safety 2: 121.

25. Vogelstein B (2013) Cancer genome landscape. Science 339: 1546-1558.

26. Lu DY, Lu TR, Xu B, Che JY, Wu SY, et al. (2018) Anti-metastatic drug development, work out towards new direction. Medicinal Chemistry 8: 512.

27. Lu DY, Lu TR, Xu B, Yarla NS (2018) Anticancer drug developments, challenge from historic perspective. EC Pharmacology & Toxicology 6: 922-936.

28. Lu DY, Lu TR, Chen EH, Yarla NS, Xu B, et al. (2018) Keep up the pace of drug development evolution and expenditure. Cancer Rep Rev 2: 165.

29. Lu DY, Lu TR, Chen EH, Xu B, Yarla NS, et al. (2017) Anticancer drug development, system updating and global participation. Current Drug Therapy 12: 37-45.

30. Komarova NL (2006) Mathematical modeling of tumorigenesis, mission possible. Current Opinion in Oncology 17: 39-43.

31. Khalil C (2006) System biology for cancer. Current Opinion in Oncology 17: 44-48.

32. Bentley DR (2004) Genomes for medicine. Nature 429: 440-445.

33. Collins F (2010) Has the revolution arrived. Nature 464: 674-675.

34. Venter JC (2010) Multiple personal genomes await. Nature 464: 676-677.

35. Lander ES (2011) Initial impact of the sequencing of the human genome. Nature 470: 187-197.

36. Maher B (2011) Genomes on prescriptions. Nature 478: 22-24.

37. Braggio E, Egan JB, Fonseca R, Stewart AK (2013) Lessons from next-generation sequencing analysis in hematological malignancies. Blood Cancer J 3: 127.

38. Knight ZA, Shokat KM (2007) Chemical genetics: where genetics and pharmacology meet. Cell, 128: pp. 425-430.

39. Lu DY, Lu TR, Ding J (2007) Employing new mathematical models and equations to evaluate risk-benefit criteria of clinical therapeutics. OnLine Journal of Biological Sciences 7: 1-2.

40. Hu PZ, Bader G, Wigle DA, Emili A (2007) Computational prediction of cancer-gene function. Nature Reviews - Cancer 7: 23-34.

41. Komarova NL (2006) Mathematical modeling of tumorigenesis, mission possible. Current Opinion in Oncology 17: 39-43.

42. Khalil G, Hill C (2006) System biology for cancer. Current Opinion in Oncology 17: 44-48.

43. Foster TS, Miller JD, Boye MK, Blieden MB, Gidwani R, et al. (2011) The economic burden of metastatic breast cancer: a systematic review of literature from developed countries. Cancer Treatment Reviews 37: 405-415

44. Lu DY, Lu TR, Xu B, Ding J, Yarla NS (2017) Clinical cancer therapy, personalized chemotherapies. J Cell Dev Biol 1: 5.

45. Lu DY, Lu TR, Xu B, Ding J, Yarla NS. (2018) General topics in the field of personalized cancer therapy. Metabolomics 8: 156.

46. Gupta GP, Massague J (2006) Cancer metastasis: building a framework. Cell 127: 679-695.

47. Talmadge JE, Fidler IJ (2010) AACR centennial series: The biology of cancer metastasis: historical perspective. Cancer Res, 70: 5649-5669.

48. Valastyan S, Weinberg RA (2011) Tumor metastasis: molecular insights and evolving paradigms. Cell 147: 275-292.

49. Lu DY, Lu TR, Cao S (2012) Cancer metastases and clinical therapies. Cell & Developmental Biology 1: 110.

50. Lu DY, Lu TR, Wu HY (2013) New insights into individualized antimetastatic therapy. Advanced Techniques in Biology & Medicine 1: 106.

51. Lu DY, Lu TR, Wu HY, Cao S (2013) Cancer Metastasis treatments. Current Drug Therapy 8: 24-29.

52. Lu DY, Xi YC (2012) Antimetastatic therapies according to metastatic cascade. Adv Pharmacoepidemiology & Drug Safety 1: 107.

53. Ruggeri BA, Camp F, Miknyoczki S (2014) Animal models of disease: Preclinical animal models of cancer and their applications and utility in drug discovery. Biochemical Pharmacology 87: 150-161.

54. Yakisich JS (2012) Challenges and limitations of targeting cancer stem cells and/or the tumour microenvironment. Drug and Therapy Study 2: 10.

55. Lu DY, Lu TR, Ding J, Xu B, Che JY, et al. (2015) Anticancer drug sensitivity testing, a historical review and future perspectives. Current Drug Therapy 10: 44-55.

56. Lu DY (2014) Drug sensitivity testing. Personalized Cancer Chemotherapy, An Effective Way for Enhancing Outcomes in Clinics. Ed, Lu DY, Chapter 2, pp5-12, Woodhead Publishing, Elsevier, UK 2014.

57. Volm M, Efferth T (2015) Prediction of cancer drug resistance and implications for personalized medicine. Frontiers in Oncology 282.

58. Lu DY, Lu TR, Xu B, Ding J (2015) Pharmacogenetics of cancer therapy: breakthroughs from beyond? Future Science OA 1.

59. Park TS, Donnenberg VS, Donnenberg AD, Zambidis ET, Zimmerlin L (2014) Dynamic interactions between cancer stem cells and their stromal partners. Current Pathology Reports 2: 41-52.

60. Magee JA, Piskounova E, Morrison SJ (2012) Cancer stem cells: impact, heterogeneity, and uncertainty. Cancer Cell 21: 283-296.

61. Visvader JE, Lindeman GJ (2008) Cancer stem cells in solid tumours: accumulating evidence and unresolved questions. Nat Rev Cancer 8: 755-768.

62. Li Y, Laterra J (2012) Cancer stem cells: distinct entities or dynamically regulated phenotypes? Cancer Res, 72: 576-580.

63. Pavelic SK, Sedic M, Bosnjak H, Spaventi S, Pavelic K (2011) Metastasis: new perspectives on an old problem. Mol Cancer 10: 22.

64. Chaffer CL, Weinberg RA (2011) A perspective on cancer metastasis. Science 331: 1559-1564.

65. Lu DY, Lu TR, Cao S (2013) Drug combinations in cancer treatment. Clinical Experimental Pharmacology 3: 134.

66. Lu DY, Chen EH, Ding J, Xu B, Lu TR. (2015) Anticancer drug combinations, a big momentum is needed. Metabolomics 5: 139.

67. Lu DY, Chen EH, Wu HY, Lu TR, Xu B, et al. (2017) Anticancer drug combination, how far we can go through? Anticancer Agents Med Chem 17: 21-28.

68. Lu DY, Lu TR, Yarla NS, Wu HY, Xu B, et al. (2017) Drug combination in clinical cancer treatment. Reviews on Recent Clinical Trials 12: 202-211.

69. Lu DY, Wu HY, Yarla NS, Xu B, Ding J, et al. (2018) HAART in HIV/AIDS treatments, future trends. Infectious Disorders-Drug Targets 18: 15-22.

70. Lu DY, Che JY, Yarla NS, Zhu H, Lu TR, et al. (2018) Type 2 diabetes study, introduction and perspective. The Open Diabetes Journal 8: 13-21.

71. Lu DY, Che JY, Yarla NS, Wu HY, Lu TR, et al. (2018) Type 2 diabetes treatment and drug development study. The Open Diabetes J 8: 22-33.

72. Madhavan D, Cuk K, Burwinkel B, Yang RX. (2013) Cancer diagnosis and prognosis decoded by blood-based circulating microRNA signatures. Frontiers in Genetics 4: 116.

73. Lu DY, Lu TR, Chen XL (2012) Individualized cancer chemotherapy, are we ready for that yet? Metabolomics 2: 113.

74. Lodhia KA, Tienchaiananda P, Haluska P (2015) Understanding the key to target the IGF axis in cancer; a biomarker assessments. Front Oncol 2015: 142.

75. Blagden SP (2015) Harressing pandemonium: the clinical implications of tumor heterogeneity in ovarian cancer. Front Oncol 2015: 149.

76. Heppner GH,Dexter DI, Denucci T, Miller Fr, Calabresi P (1978) Heterogeneity in drug sensitivity among tumor cell subpopulations of a single mammary tumor. Cancer Res 38: 3758-3763.

77. Lu DY, Lu TR, Che JY, Yarla NS (2018) Individualized cancer therapy, what is the next generation? EC Cancer 2: 286-297.

78. Lu DY, Lu TR, Che JY, Shen Y, Yarla NS, et al. (2018) Individualized cancer therapy, future approaches. Current Pharmacogenomics & Personalized Medicine 16: 156-163.