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Submission to Academia Letters

Precision Medicine Approach to Signal Based Targeted Therapy of Cancer

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Abstract: The genetic changes appearing in the information system of the cells that program its unregulated growth and proliferation gradually lead to cancer manifestation and the treatment options must be guided accordingly. The critical roles played by some of the molecules associated with the specific signaling pathways and cell microenvironment that lead to oncogenesis and metastasis have been described precisely in recent years based on findings of the human genome project. Thus, precision oncology that relies on the genomic study of the cancer cells to better understand the prognosis and pathways involved with disease progression for the cure is destined to serve the purpose adequately. This article intends to comprehensively elucidate the foundations and frontiers of precision oncology in the context of recent advances in the field of cancer genomics and single-cell technology for efficient cancer treatment.

Key Words: Gene Mutation, Gastric Cancer, p53, K-Ras, Cancer Genomics, Targeted Therapy, Immunotherapy

Introduction: Cancer remains the leading cause of death and it has a major impact on society across the world. The fundamental abnormality resulting in the development of cancer is the continual unregulated proliferation of cancer cells. Alterations in the overall expression pattern of the genes responsible for

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the regulation of cell growth and proliferation may lead the development to go awry and the factors that cause genetic changes tend to provoke the development of cancer. Every single gene is likely to have undergone mutations on an innumerable number of occasions with a repair mechanism in place to sustain deleterious mutations in genes that regulate cell growth and division. In this way, the generation of cancer has to be linked to mutagenesis; the introduction of a change in the DNA sequence by the external agents called mutagens and yet a single mutation is not likely to be enough to change a normal cell into a cancer cell as it will require several changes to accumulate with time for cancerous development to take place. For example, mitogenic stimulation due to mutations in Ras or Myc will not lead to unchecked proliferation till the changes in genes that encode essential components of the protective mechanisms, such as Arf or p53 have not occurred alongside. As a matter of fact, most cancers derive from a single abnormal cell with certain unwanted gene mutations when additional changes accumulate in some of the descendants of the cell allowing them to outgrow their neighbors leading to tumor growth in the end. Cancers can also be driven by epigenetic dysregulation in the form of certain persistent changes in the gene expression pattern due to modifications of chromatin structure often led by DNA methylation or histone modification without accompanying alteration of the cell's DNA sequence. Further, the population of cells that make up cancer is profoundly heterogeneous at the genetic, and epigenetic levels and mainly because the cancer genome is found unstable. Finally, the gene mutations that alter the DNA sequence of the affected cells appear to be at the source of all changes in the cell behaviors and remain the most fundamental and universal feature of cancers, and hence it is to be seen as a genetic disease. In this way, 'precision oncology' that relies upon molecular profiling of tumors to identify targetable alterations for individualized treatment of cancer appears to be a means to the end1.

The emergence of Cancer Genomics: There are many types of treatment available such as chemotherapy, targeted drug therapy, radiation therapy, surgery, stem cell transplant, immunotherapy, hormonal therapy, etc. and some people may receive a single type of treatment and some will have a combination of treatments but whatever be the regimen the result must be a cure. In the past few decades, technological advances in molecular biology have proven

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invaluable to understanding the pathogenesis of human cancer. The emergence of next-generation sequencing (NGS) since 2005 has proved to be massively important in this direction as the technology is used to determine the order of nucleotides in entire genomes or targeted regions of DNA or RNA and has in fact revolutionized the biological research allowing scientists to study biological systems at a level never before possible in reality. It is providing new insights into the nature of genes and proteins thought to be associated with cancer and the application of such evolving molecular techniques to the study of cancer has not only led to advances in tumor diagnosis but has also provided markers that are proving to be the means for a better assessment of prognosis and disease progression. Historically, cancer treatments like chemotherapy and radiation therapy have been targeting actively growing cells of the tissue instead of just attacking diseased cells, and the need for a deeper understanding of the signaling pathways and associated molecular events that remain active during cancer progression has been realized for developing treatments that target the affected cells alleviating the serious side effects of cancer treatment. The functional roles of many critical players involved in tumor growth, tissue invasion, and metastasis have been described precisely in recent years due to the draft of the human genome and many other related discoveries. The protein K-Ras is mutated in about 90% of pancreatic ductal adenocarcinoma cases and about 40-50% of human cancers carry deleterious mutations in the p53 gene. The treatment of pancreatic ductal adenocarcinoma (PDAC), the most common form of pancreatic cancer with the leading cause of cancer-related death has largely been unsuccessful due to the tumor microenvironment which exhibits an ample amount of stromal cells and a complicated extracellular matrix. The genomic analysis has recently revealed that PDAC harbors frequently mutated genes that include KRAS, TP53, CDKN2A, and SMAD4, which can widely alter cellular processes and change the tumor microenvironment which in turn, affects cancer progression. Mammalian cells express three distinct but closely related Ras proteins (K-RAS, H-RAS, and N-RS), which may become mutationally activated and promotes oncogenesis. The mutation frequency of different Ras in human cancers varies, and K-Ras is found to be the most frequently mutated isoform leading to uncontrolled cell proliferation, migration, and invasion in many cancers. The euphoria created two years ago with the development of drugs that

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could block K-RAS was lost sooner like many other targeted cancer drugs as the affected cells became resistant to the inhibitors, a common problem encountered with drugs designed for targeted cancer therapy. The study of K- RAS resistance mechanisms reveals researchers may have to try several different drug combinations to overcome the problem and some of these are in the pipeline2. Researchers are tirelessly working to figure out how to target K-RAS and other signaling proteins behaving abnormally in different cancer cells to develop novel therapeutic options. Some breakthroughs have occurred in certain cancer types where understanding of the cell signaling has led to the development of specific targeted drugs that have really revolutionized the treatment of cancer.

Signaling Pathways Dysregulation as the Prospective Targets for Cancer Treatment: The emerging understanding of the molecular basis of cancerous cell behaviors recognizes that cancer is a signaling disease. Tumors and cancer are mainly the results of uncontrolled cell division. Normally, cell division is regulated by a family of extracellular growth factors, the proteins that cause resting cells to divide by exploiting the signaling process of the cell. As the foremost system of communication, a cell signaling network that involves many of the secreted protein receptors, cytoplasmic proteins and kinases, growth factors, and nuclear transcription factors, enables individual cells to respond to extracellular signals with physiologically appropriate behavior. Cell signaling mainly allows normal cells to sense whether their state of attachment to the extracellular matrix and other cells is appropriate and if different growth factors, hormones, and cytokines guide them to proliferate or differentiate, move or stay put, or commit to cell death by apoptosis or autophagy. The oncogenic mutations basically disrupt the signaling circuits that control cell adhesion and signaling, enabling cells that carry them to proliferate and invade the other tissues in an uncontrolled fashion against the requirements. Many oncogenes are mutated forms of cellular proto-oncogenes that otherwise encode normal proteins participating in signal transduction pathways. Negatively acting tumor suppressor genes mostly act to maintain balance in product formation by modifying the signaling pathways and are the actual targets for the action of signaling molecules. Thus, many oncogenes are activated versions of signaling proteins whereas many tumor suppressors normally repress signaling. Because cancer progression frequently involves altered signal transduction pathways ow-

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ing to mutations in the concerned genes, it is satisfying as well as mechanically well-founded that therapeutic interventions taking account of this biology might pave the way for a far more effective treatment of cancer and therefore therapeutic substances that target the signal transduction process are constantly being explored as the prospective and efficacious agents for cancer treatments3. These therapeutic agents are the anticancer drugs designed to target molecules directly involved with the signaling processes or related molecules in the tumor microenvironment and essentially required for tumor growth and cancer progression. They are broadly classified as monoclonal antibodies or small molecule drugs. The therapeutic monoclonal antibodies (mAbs) targets antigen found on the cell surface and the small molecules can penetrate the cell membrane to interact with targets inside the cell and are usually designed to inhibit the enzymatic activity of the target proteins like the proteasome complex, tyrosine kinases or cyclin-dependent kinases. The signal transductions leading to tumor growth, cancer cell migration, metastasis, and drug resistance are often complex processes, and cancer cells can harbor abnormalities in multiple signal pathways and can rely on redundant signaling pathways as well for unregulated growth and survival. The constitutive activation of molecular intermediates that are responsible for cancerous developments can sometimes be sustained by different mechanisms and combination therapy that inhibits multiple targets or redundant pathways simultaneously with therapeutic agents may be the most effective way to treat and overcome resistance in cancer therapy.

Single Cell Technology for Unmasking Tumour Heterogeneity: The important part of tumorigenesis is that cancers of different tissues utilize somewhat different patterns to converge to a relatively common path of cancer development witnessed as tumor growth followed by angiogenesis and metastases. Such a development is ultimately guided by gene mutations associated with the cancer cells and tissue-specific factors that help the tissue exploit the genetic changes manifested as the specific pathways utilized by different cancers and so no gene change is common to all cancers. As the tumors are often a very heterogeneous mixture of distinctly differentiated cancer cells that include connective tissue cells, immune cells, cancer stem cells, and vasculature, more precisely the cellular composition of a tumor is known and the mechanisms involved with the diseased cells are understood the more specific targeting strategies could be

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devised to treat the disease. The rapid progress in the development of next-generation sequencing (NGS) technologies in recent years has provided many valuable insights into cancer genomics in recent time. NGS-based technologies for genomics, transcriptomics, and epigenomics are becoming important tools to help carry out single-cell measurements within the tissue as they can provide a clear picture of the complex biological processes and unmask heterogeneity present in the tumor mass. Single-cell genomics can facilitate the simultaneous measurement of thousands of genes in thousands of 'single' cells from a single specimen allowing researchers to compare the genomes of individual cells within the tissue to determine the mutation profile of the cells influencing the changes in the tumor microenvironment. The advances in these techniques and relevant computational approaches can help integrate genomic and transcriptomic data to reveal the most accurate information on the activity state of individual genes to help detect novel cancer drivers and genetic vulnerabilities and provide an unprecedented insight into the complex genetic and epigenetic heterogeneity within individual tumors for advanced precision oncology. The importance of epigenetic reprogramming in cancer is evidenced by the fact that chromatin regulators are often mutated and the widespread epigenetic changes throughout cancer genomes can be identified and linked to the activity of known tumor promoters or suppressors genes such as growth factors stimulated genes or TP53, etc. The premise of epigenetic profiling holds great possibilities for deciphering the cellular states and characterizing phenotypic heterogeneity. The targeted therapies may try to pin specific mutations that have a profound effect on epigenetic pathways and the inclusion of epigenetics in clinical practice will require the identification of epigenetic signatures that mediate distinct phenotypical changes of clinical relevance such as mesenchymal transition, stemness, dormancy, and quiescence or therapy resistance. Thus the molecular analysis of cancer cells now aims to present a precise picture of the most up-to-date development in the tumor microenvironment and detection of changes in the genes and proteins responsible for alterations in the cellular processes towards the manifestation of cancer. The ability to demonstrate the role and function of distinct cell types comprising the tissues using single-cell technologies is paving the way for a new understanding of the tissue-specific cellular pathways and interactions that lead to cancerous developments, it is going to be of great im-

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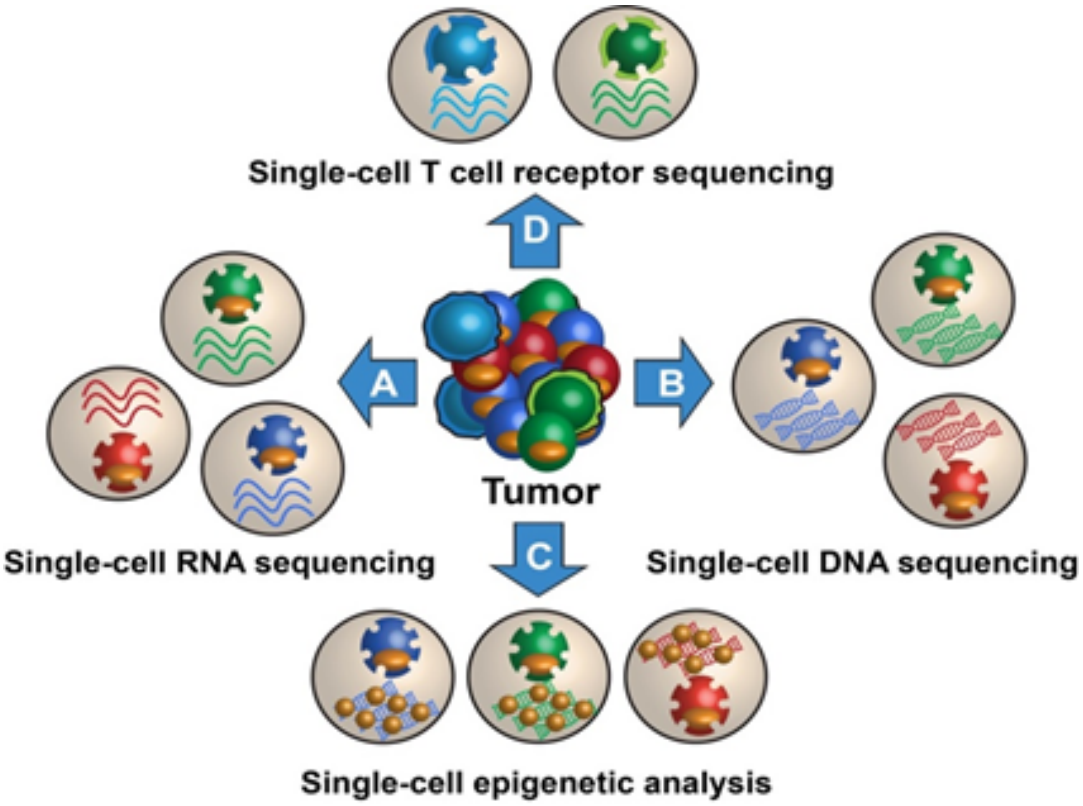
portance in strategizing the treatment of cancer and is thought to streamline future research directions.



Single-Sell analysis of tissue for the study of cancer heterogeneity

Precision Oncology in Targeted Therapy: Targeted therapy is now the accepted form of cancer treatment that targets specific genes and proteins of the cancer-related signaling pathways and the molecules in the tumor microenvironment that contribute to cancer development and is contrary to the single target approach employed in chemotherapy to primarily target and kills the actively dividing cancer cells with serious side effects. A type of targeted therapy, called rumor agnostic therapy uses drugs and other substances to target certain genetic changes or markers as the cancer-specific features to treat the ailment without requiting to focus on the cancer type or where cancer may have started

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in the body. The use of monoclonal antibodies (mAbs) in targeted therapy is being explored as well as they may be exploited successfully for potentiating the natural immune system and addressing the concern related to change in immunogenicity of the cancer cells. The mAbs may be designed to coat the cancer cells to be recognized and destroyed by the immune cell or block the activity of certain abnormal proteins in the affected cell or inhibit the immune checkpoints that help cancer cells escape or survive the immune responses. In this way, targeted drug therapy and monoclonal antibody-based therapy need to be seen as the potent means for cancer treatment and are becoming increasingly crucial in cancer therapy, they will serve the needs better if the treatment is tailored to the requirements of the selected group of people or individuals receiving treatment for the disease. The field of cancer genomics emerging as the new branch of cancer research is directed at strategizing targeted therapy by exploiting the peculiarities of the cancer genomes of the individuals for an efficient treatment. It is dedicated to studying the genetic profile of cancer cells aimed at gaining a thorough understanding of the signaling pathways and related molecular events in the course of tumor growth, cell migration, invasion, and metastases, and to the fuller understanding of drug resistance for proper treatment of cancer. The Cancer Genome Atlas (TCGA), a landmark cancer genomics program started in 2006 has contributed immensely in realizing the importance of cancer genomics to our understanding of cancer in the last decade and has begun to change the way the disease has to be treated in the clinic4. The challenge to identify the relevant genes and signaling molecules for each cell type using cutting-edge technologies will remain the essential part of cancer research and the use of cancer genomics-based selection of regimen will allow reaping the fruits of the researches swiftly in cancer treatment.

Precision Oncology Based Treatment in the Age of Cancer Genomics

Conclusion: Precision oncology based on cancer genomics proposes to develop treatments that target the specific molecular characteristics of an individual's tumor instead of targeting the common features of particular cancer for a proper cure. A thorough understanding of the genetic composition and heterogeneity of the individual's tumor is now becoming possible through the single-cell technologies and it can help the individuals get the right treatment within

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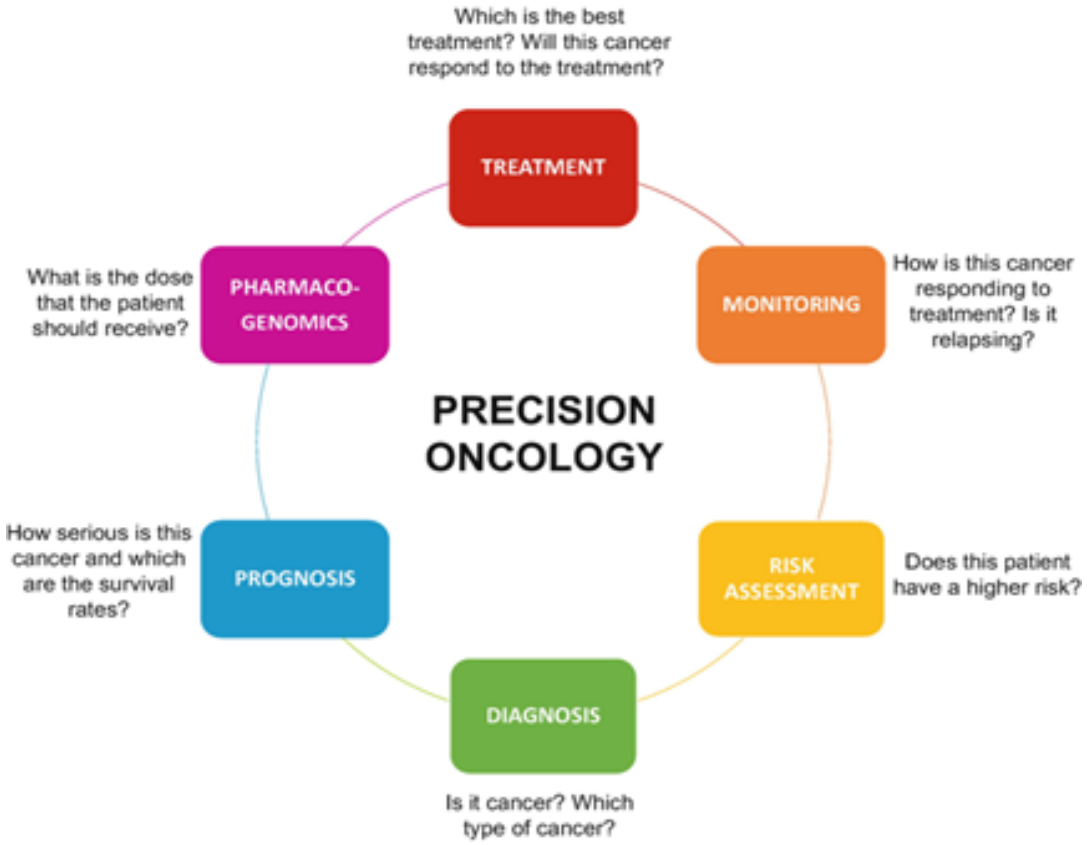

the range of possibilities rather successfully without requiring to go through more conventional methods of treatment that might not prove most effective at the end. In this way, precision oncology emerging as a new field of cancer treatment based on the identification of specific mutations in the genes to selectively target the pathways associated with the changes appear to be the natural outcome of cancer genome research and is likely to satisfy the intended purpose of the project satisfactorily. The success of this form of treatment is sure to further strengthen our belief in the possibility of a cure for cancer and is needed to be accessible to the larger number of people with cancer towards the realization of goals with time.

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