RESEARCH ARTICLE

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CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 16, Issue, 01, pp.061-068, January, 2025

International Journal of Recent Scientific Research

ISSN: 0976-3031

Subject Area : Medical Science

IDENTIFICATION OF POTENTIAL THERAPEUTIC TARGETS FOR THE DEVELOPMENT OF NOVEL TREATMENT STRATEGIES IN DISEASE MANAGEMENT

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DOI: http://dx.doi.org/10.24327/ijrsr.20251601.012

ARTICLE INFO

Article History:

Received 10th December, 2024
Received in revised form 20th December 2024
Accepted 18th January 2025
Published online 28th January, 2025

Key words:

chronic myeloid leukemia, BCR-ABL, tyrosine kinase inhibitors, drug resistance, synthetic lethality

ABSTRACT

Over the course of the last ten years, targeted small molecule medications have brought about a significant change in the treatment of chronic myeloid leukemia (CML). These medications disrupt the ATP-dependent ABL tyrosine kinase, which in turn disrupts a constitutively active BCR-ABL, which is the agent that is responsible for chronic myeloid leukemia. Despite the fact that tyrosine kinase inhibitors (TKIs) have been shown to be helpful in facilitating a survival rate that is more than 90 percent, these medications do not have any curative effects. In addition to this, the T315I BCR-ABL variant is ineffective against all of the TKIs that are currently licensed. A new generation of TKIs that are capable of binding to T315I is on the horizon, however. The current therapeutics for chronic myeloma, such as TKIs of the first and second generations, as well as potential future therapy techniques, will be reviewed, with a particular focus on the clinical utility of these medications. In recent years, new insights have emerged on the complexity of chronic myelogenous leukemia, notably in the microenvironment of the bone marrow. As a result of the fact that primitive human CML stem cells are not dependent on BCR-ABL, we recommend that strategies that go beyond targeting BCR-ABL will be the key to successfully treating CML. For patients suffering from chronic myeloid leukemia, the use of synthetic lethality or combinations of medications has the potential to transform responses into therapies that are permanent.

INTRODUCTION

By making the discovery of microRNAs (miRNAs) in 1993, Victor Ambros1 and his groups from Harvard University contributed to the achievement of a new milestone in the field of study. Lin-4, which comprises sequences that are complementary to a repeating sequence motif in the 3' untranslated region (UTR) of the lin-14 mRNA from Caenorhabditis elegans, was the first microRNA gene to be found.1. After then, lin-4 was regarded as a discovery in the field of worm genetics. On the other hand, it wasn't until the discovery of a second miRNA called let-7 that it was discovered that miRNAs are highly conserved across all animal species, including humans.Two, three The investigation and creation of several microRNAs in C. elegans, Drosophila, and human cell lines, particularly in HeLa cells, was facilitated as a result of this finding. Numerous studies that relate miRNA dysregulation with human illness have been published as a result of the increasing research on microRNAs; one such study was released in the year 2002. Calin et al. report two human miRNA genes, mir-15a and mir-16-1, that are often deleted or downregulated in chronic lymphocytic leukemia (CLL) illnesses. These genes are described in this paper. At this time, thousands of microRNAs have been discovered in a variety of organisms, including humans, plants, and animals. In 2011, Kozomara and Griffiths-Jones5 reported that a total of 18,226 microRNAs were discovered in various organisms, including viruses, plants, and mammals. Furthermore, they found that the human genome had 1,921 miRNAs that were encoded. Miravirsen, a short locked nucleic acid (LNA) for miR-122, is now making its way into the market, which is a significant development since it happens to be the world's first miRNA treatment. For the treatment of hepatitis C virus (HCV) infection, this medication is now being tested in clinical studies that are at the phase II stage.6.

When it comes to target-specific gene silencing by RNA interference (RNAi), small interfering RNA (siRNA) is a

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powerful instrument. In the year 1998, Craig Mello and his colleagues made the first observation that RNA interference (RNAi) might silence genes in C. elegans. In 2006, Mello and Fire were awarded the Nobel Prize in order to recognize their achievement. RXi Pharmaceuticals is a firm that specializes in the development of RNAi drugs, and Dr. Craig Mello is one of the founders of the company. The capacity of RXi Pharmaceuticals Corporation's compounds to "self-deliver," which means that they do not need any extra delivery vehicles for particular targeting, is the most essential concept that underpins the company.) RNAi treatments are now being monitored by "Big Pharma" corporations, who are keeping an eye on the developments in clinical trials.

There have been roughly twenty clinical studies that have been started employing treatments based on miRNA and siRNA as of this moment. These medications are being developed by four of the most successful RNA-therapeutic firms, which are operating platforms. The substance SPC3649 (miravirsen), which is an inhibitor of miR-122 and was produced by Santaris Pharma from Denmark, is the only miRNA therapy that has been entered into a clinical study that is now being conducted. Preclinical testing is now being conducted for a number of additional miRNA therapies, with the ultimate goal of entering clinical trials. On the other hand, a number of treatments based on siRNA have been put through clinical trials. To a certain extent, experts are of the opinion that microRNAs are classified as RNA interference-based treatments.ten Both the synthesis and the mechanism of action of microRNAs are relatively comparable to those of siRNAs in terms of their ability to silence genes after transcription has taken place. It has been shown that microRNAs are small RNAs that are produced by the body and work in conjunction with Argonaute proteins to control the expression of genes. These two groups of short RNAs are significant for the gene regulatory landscape in the modern scientific world because they are considered to be relevant at the translational level. mRNAs are known to act as regulators of genes that are found in the body. On the other hand, siRNAs contribute to the preservation of genomic stability. Both of these forms are single-stranded, and it was discovered that they are associated with effector associations that are known as RNA-induced silencing complexes (RISCs). On the other hand, the mechanisms of action of miRNA and siRNA are distinct from one another due to the fact that each of these ribonucleic acids have distinct patterns of behavior. In order to find target mRNA sequences and make use of their inhibitory actions on the translation process, microRNAs typically employ eight nucleotides from their 5' end. In contrast, small interfering RNAs (siRNAs) recognise target sequences and facilitate cleavage of the target messenger RNA (mRNA) by using nearly their complete lengths.

A comprehensive analysis of the patent landscape of therapeutic miRNAs and siRNAs is presented in this research. Here, we discuss the key siRNAs and miRNAs that are now available in the therapeutic landscape, as well as the therapeutic methods that may be used by these molecules. Additionally, we concentrate on the parent biopharmaceutical firms of these businesses as well as the current progression of their preclinical and/or clinical studies. In the course of the conversation, a few of the bottlenecks that are involved have been brought to light. In conclusion, we also made an effort to improve our understanding of the basic perspectives of pharmacokinetics, pharmacodynamics, and effective delivery strategies for therapeutic RNAs.

OBJECTIVE

1. To find possible areas for treatment.
2. To find new ways to treat existing diseases by identifying possible therapeutic targets.

Patent Landscape for Therapeutic miRNAs and siRNAs

There is a possibility that patent rights may become more important to the innovation industry as time goes on. In the past, it has been common practice to award patents for innovations that are not related to medications. Methods that have recently been found in current biology, such as monoclonal antibodies and rDNA protocols, are examples of techniques that might be protected by patents.Small-molecule medicines and biological therapeutic potential have also been included in the scope of patents under consideration. As a direct result of this lawsuit, academic software and hardware were made available to professional businesses. The government has granted licenses to private enterprises for the use of a variety of biomolecules. At the present, the biopharmaceutical industry and the biopharmaceutical industry as a whole are very reliant on innovation and patents. During the course of the last 10 years, the number of patents that have been awarded to biopharmaceutical companies has seen a rather significant increase. Because of this, obtaining patents for treatments that are based on short RNA is a primary priority. The ability of any firm to protect its patents via the use of well-licensed applications is another factor that defines the market value that the company may get from the enabling technology. Corporations are required to preserve these concepts as trade secrets in order to retain a competitive advantage in industries where the technology for miRNA or RNAi is restricted.

In accordance with the International Patent Classification (IPC) codes, the patent search conducted using the Delphion database produced a total of 1,661 American patent papers that were related to miRNA. Laitala-Leinonen conducted an analysis of the existing patent applications that were related to miRNA biology and provided a full explanation of the method. More than sixty different IPC code groups are included in the patent applications that deal to microRNAs. Nearly half of all patents that are submitted in the United States include pharmaceutical preparations that contain miRNA-modulating chemicals or methodologies that incorporate miRNA-modulating activity for the purpose of treating diseases. A greater number of patents relating to cancer treatment techniques are specified by the researchers than patents referring to any other illness or condition. There were less than ten percent of all patents that were issued for ailments that were not the one in question. Furthermore, the authors provide evidence that the year 2008 saw the submission of the very first

patent in Europe that was based on miRNA. In spite of this, we found out via the Google Scholar database that an American patent (US 20070092882 A1) was granted for the purpose of miRNA analysis. It has been noticed that several universities, research institutions, and pharmaceutical businesses from all over the globe submitted the first patent applications for certain miRNAs. A number of institutions in Asia, including the College of Medicine, Pochon Cha University Industry-Academic Cooperation Foundation in Gyeonggi-do, South Korea, and the Council of Scientific & Industrial Research in India, as well as an Israeli company called Rosetta Genomics in Western Asia, are among these institutions. The Max Planck Society for the Advancement of Science in Germany, the University of Massachusetts, the Massachusetts Institute of Technology, and Rockefeller University in the United States are also among these institutions. Several companies, including Regulus Therapeutics and Stanford University, have been successful in obtaining patents for miRNA functional analysis methodologies and anti-miRNAs that have improved activity and efficacy. Utility Guidelines were published by the United States Patent and Trademark Office (USPTO) in 2001 as a reaction to the controversy that has been going on since the late 1990s about the patentability of gene sequences.

Identification and inhibition of key regulatory networks

SIRT1, p53, and MYC

Cell cycle and cell death are both regulated by the p53 protein, which is a key modulator. The NAD+ dependent deacetylase SIRT1, which is required for the regulation of p53, is overexpressed in human CML leukemic stem cells. It was shown that pharmacological inhibition of SIRT1 or knocking down SIRT1 led to an increase in apoptosis and CP CML LSC depletion. The combination of SIRT1 and TKIs resulted in an increase in impact.22. An increase in p53 acetylation and transcriptional activity was seen in CML progenitors when SIRT1 was inhibited. The inhibitory effects of SIRT1 targeting on CML cells were reliant on p53 expression and acetylation. There is a possibility that blocking SIRT1 might be a method to activate p53 and target CML leukemic stem cells. There is an alternative approach for activating p53, which involves inhibiting the connections that p53 has with HDM2, which is its negative regulator. The small-molecule inhibitor MI-219 was able to reduce the number of cases of chronic myelogenous leukemia (CML) in both laboratory and animal trials without having an effect on normal primitive progenitors. In light of these results, it would seem that a medication that activates p53 might potentially be an effective target for CML leukemic stem cells.

Holyoake and colleagues employed proteomics, transcriptomics, and network investigations to reveal that p53 and c-MYC are significant nodes that govern faulty protein synthesis in human CML LSCs. These nodes are linked and control the pathways that lead to abnormal protein production.a 24 MDM2 and BET inhibitors were used in conjunction with one another to induce an increase in the p53 apoptotic pathway and a decrease in the expression of c-MYC in laboratory mice. This resulted in the selective death and near-eradication of transplantable human LSCs in mice, while normal HSCs were spared. The use of an impartial systems approach makes it simpler to identify critical targets for LSC targeting, as shown by these studies.

FOS and DUSP1

C-FOS and DUSP1 expression were shown to be convergently elevated by BCR-ABL kinase and growth factor signaling, according to the findings of a gene expression research conducted by Azam and colleagues under his supervision. In a BCR-ABL animal model of chronic myelogenous leukemia, these genes played a significant role in the growth of tumors. A number of in vivo experiments, including those in which mice were xenotransplanted with human CML cells, indicated that the elimination of minimal residual disease (MRD) was achieved by the pharmacological inhibition of c-FOS and DUSP1. Following the completion of their investigation, they came to the realization that c-FOS and DUSP1 need to be the targets of therapeutic interventions in the battle against LSCs. It is fascinating to learn that this procedure was carried out in a significant number of kinase-driven leukemias.

Autophagy inhibition

In patients with chronic myelogenous leukemia (CML), treatment with TKIs induces autophagy, which is associated with stress on the endoplasmic reticulum and an increase in the flow of intracellular calcium. The TKI-induced cell death in primary CML cells was enhanced by pharmacological inhibitors or RNA interference that decrease autophagy. Additionally, CML stem cells were removed. As a way of enhancing the effectiveness of targeted immune-modulatory medicines (TKIs), hyperchloroquine administered intramuscularly is now being evaluated as part of a trial for chronic myeloid leukemia (CHOICES). Despite the fact that the experiment has been carried out, the results have not yet been disclosed.

Resistance mechanisms to TKI therapy in CML

Two of the most common classifications for TKI resistance are referred to as “primary resistance” and “secondary resistance.” Both of these classifications take into consideration resistance mechanisms that are either dependent on or independent of BCR-ABL1. Two of the most common classifications for TKI resistance are referred to as “primary resistance” and “secondary resistance.” Both of these classifications take into consideration resistance mechanisms that are either dependent on or independent of BCR-ABL1.

Despite the fact that there is no data that directly links these mechanisms to TKI resistance, they have been hypothesized as possible reasons of disease progression in chronic myelogenous leukemia (CML). Telomere length, variable gene expression, proteins that affect transcription, BCR-ABL1-mediated genetic instability, telomere expression, and the BCR-ABL1 transcript are some of the factors that are considered to be genetic instability. CML is a difficult disease to treat because individuals might acquire resistance to TKI via either the

BCR-ABL1 dependent route or the BCR-ABL1 independent pathway. This makes the management of CML more difficult. Mutations that prevent TKI binding in the ABL kinase domain, oncogene amplification in the BCRABL1 gene, and increased levels of BCR-ABL1 messenger RNA are some of the therapeutic approaches that are dependent on BCR-ABL1. An increase in the activity of drug efflux pumps, a decrease in the activity of drug influx transporters, an increase in the expression of the Src-family kinase protein Lyn, and activation of survival pathways such as the STAT3 pathway, the PTKB/mammalian target of rapamycin pathway, and the RAP/ERK/NF pathway are all examples of pathways that are independent of ABL1. Specifically, the latter processes provide insight on the reasons why leukemic stem cells (LSCs) diagnosed with chronic myelogenous leukemia are resistant to TKIs.

TKIs are able to greatly suppress the proliferation of LSCs, despite the fact that they only produce modest apoptosis. When it comes to quiescent LSCs, the elimination and apoptosis that are brought about by TKIs are extremely challenging to resist. It has been shown via research that TKIs have the ability to effectively block kinase activity inside LSCs. This finding suggests that LSC resistance is not reliant on BCR-ABL1 kinase action. The research that has been conducted on chronic myeloid leukemia (CML) during the last fifteen years has been determined in large part by these outcomes, and experts are in agreement that the most important need in the area is to find ways to increase treatment-free remission (TFR).

Those patients with chronic myeloid leukemia (CML) who did not respond well to tyrosine kinase inhibitors (TKIs), who were tolerant of or resistant to TKIs, or who had residual disease because leukemic stem cells persisted in the bone marrow are the focus of this review, which provides a summary of what is currently known about immunological targeting approaches and ABL- and non-ABL-directed inhibitors.

BCR-ABL1 targeted therapy other than TKIs a. Asciminib (ABL001)

As opposed to other TKIs, asciminib, which is an allosteric inhibitor of ABL1, inhibits the activity of ABL1 kinase by attaching itself to the myristoyl pocket of the protein rather than the catalytic pocket occupied by the protein. BCR-ABL1 signaling is inhibited as a result of this binding process, which results in the formation of an inactive kinase configuration. It has been shown that mutations within the kinase domain of ABL1 do not give resistance to asciminib. In spite of the fact that mutations in the myristoyl pocket can render a protein resistant to asciminib, these alterations will not have any impact on the way that standard TKIs bind. Therefore, it is theoretically feasible that resistant mutations might be avoided with the use of combination therapy. A dose-escalation trial of asciminib monotherapy is being conducted in this phase I study for patients with chronic myeloid leukemia (CML) who have been treated with two or more targeted immune-modulatory medicines (TKIs) and have failed to respond to treatment. The number NCT03595917 is the identification for the trial on Clinical Trials.gov. The number of patients who participated in the trial was much higher than the number of patients who did not have any adverse reactions to three or more TKIs. In accordance with the initial results, 82 percent of the patients who were resistant to TKIs shown a significant cytogenetic response by the third month, and roughly thirty percent of the patients approached MMR by the fifth month. The medication was shown to be efficacious over a wide variety of dosages, including T315I, and it had a safety profile that was acceptable. Recent data from a phase I study (ClinicalTrials.gov number, NCT02081378) have shown that asciminib monotherapy yields superior results when administered to a patient population that is similar and has been followed for a longer period of time. A prevalence of CCyR was found to be 70% at the 12-month point, whereas the prevalence of MMR was found to be 48%. Sixty percent of patients who had a baseline BCR-ABL1IS of 0.1% or below were able to initiate or maintain a significant molecular response over the course of the study. Furthermore, a number of individuals with chronic myeloma who were thought to have ponatinib resistance or side effects that were severe were able to achieve metastatic relapse. The administration of a combination of asciminib and ponatinib was reported to improve the treatment of patients with Ph+ leukemia and to reduce the development of highly resistant BCR-ABL1 compound mutations. As an additional point of interest, the early results from the ASCEMBL investigation are still forthcoming. The purpose of this clinical study is to evaluate asciminib and bosutinib in patients with chronic myeloid-progressive illness who have previously been treated with two or more BCR-ABL1 targeting tumor kinase inhibitors (NCT03106779). This trial is a phase III clinical inquiry.

Non-BCR-ABL1 targeted therapies

Farnesyl transferase inhibitors

Farnesyl transferase inhibitors are known to impede the capacity of the enzyme to transfer isoprenoid groups to other protein targets, which is necessary for the activation of proteins such as RAS. In patients with chronic myeloid leukemia, the process of leukemogenesis is completely dependent on the presence of constitutive RAS activity. The farnesyl transferase inhibitors tipifarnib (R115777) and lonafarnib (SCH66336) have the potential to produce antileukemic effects on patients who have chronic myeloid leukemia (CML).

Tipifarnib

Tipifarnib, when administered alone, generated hematological responses (full or partial) and minor cytogenetic responses (transient) with a median duration of only nine weeks, according to the findings of twenty-two patients with chronic myelogenous leukemia with chronic granulomatous disease (CML-CP) or severe sickness who had not responded to INFα treatment. Patients with chronic myeloid leukemia (CML) who had failed treatment with imatinib were given combination therapy consisting of tipifarnib and imatinib (NCT00040105). Fifty percent of these patients exhibited mutations in the ABL kinase domain. 36% of patients had cytogenetic responses as a consequence of co-treatment, whereas 76% of patients saw

hematological responses. A BCR-ABL1 mutation was also discovered in four people who were in cytogenetic remission (CyR), which is another term for remission of cancer.

Lonafarnib

In a clinical study (NCT00038597), patients with chronic myeloid leukemia who were either unable or unwilling to utilize imatinib were the focus of an investigation of the efficacy of lonafarnib. Only two of the thirteen individuals who were enrolled had hematological responses over the course of the study. Even though the doses of lonafarnib and imatinib were different, the combination of the two drugs boosted their efficacy. Hematological and cytogenetic responses were seen in 35 percent of patients who participated in a phase I study (ClinicalTrials.gov number, NCT00047502) that studied individuals with chronic myelogenous leukemia who had not responded to imatinib treatment. When combined, lonafarnib and imatinib are safe for persons with chronic myelogenous leukemia (CML), according to the authors of the research. Because of the non-overlapping mechanisms of action that this combination has, it has the potential to give therapeutic impact in some patients who are suffering from imatinib-resistant illnesses.

As a result of these data, it is evident that individuals with chronic myelogenous leukemia did not experience significant benefits from monotherapy with farnesyl transferase inhibitors. Patients diagnosed with chronic myelogenous leukemia who do not respond to therapy with TKIs may benefit from co-administration of these drugs with imatinib.

Mammalian target of rapamycin (mTOR) inhibitors: mTOR inhibitors target the mTOR, a serine/threonine kinase regulating cellular proliferation and metabolism. Constitutive mTOR activation has been observed in different leukemia types, including CML.

i. **Rapamycin (Sirolimus):** As a result of rapamycin-induced mTOR dephosphorylation, the efficiency of imatinib is increased in cells that are resistant to the drug, and the survival rate of CML cells is lowered. As of right now, there is just one clinical trial (NCT00776373) that is investigating whether or not rapamycin, when combined with DNA-damaging medicines like cytarabine or etoposide, is effective in treating chronic myeloid leukemia (CML) types AP and BC.

ii. **Everolimus:** Everolimus inhibits the constitutive activation of mTOR, which results in a reduction in the development of CML and an increase in imatinib sensitivity. The efficacy of everolimus as a therapy for chronic myelogenous leukemia (CML) patients is now being evaluated in a variety of clinical trials, both on its own and in combination with imatinib (ClinicalTrials.gov numbers, NCT00081874 and NCT00093639). Rapamycin is not being evaluated in these studies.

CONCLUSION

TKIs that inhibit BCR-ABL1 signaling are considered the gold standard for both first-line and salvage treatment of chronic myelogenous leukemia (CML). It is possible that some people may need alternative treatment methods, such as medications that target BCR-ABL1 in addition to those that do not target this gene. Either by themselves (such as omacetaxine or asciminib) or in combination with TKIs (such as PEG-IFN-α or HMAs), these medications may be used alone or in combination. You can utilize these medications to get a response in patients who haven't gotten it with TKIs, and they can help some patients who have had the greatest outcomes with TKIs have even deeper molecular responses so that they may attempt TFR. Both of these things are possible. Over the course of the future, it will be of the utmost importance to develop solutions to the difficulties of determining the optimal timing to provide these medicines during the evolution of the disease and of successfully combining these novel medications with TKIs.

References

1. R.C. Lee, R.L. Feinbaum, V. Ambros The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14 Cell, 75 (1993), pp. 843-854
2. A.E. Pasquinelli, B.J. Reinhart, F. Slack, M.Q. Martindale, M.I. Kuroda, B. Maller, D.C. Hayward, E.E. Ball, B. Degnan, P. Müller, *et al.* Conservation of the sequence and temporal expression of let-7 heterochronic regulatory RNA Nature, 408 (2000), pp. 86-89
3. B.J. Reinhart, F.J. Slack, M. Basson, A.E. Pasquinelli, J.C. Bettinger, A.E. Rougvie, H.R. Horvitz, G. Ruvkun The 21-nucleotide let-7 RNA regulates developmental timing in Caenorhabditis elegans Nature, 403 (2000), pp. 901-906
4. G.A. Calin, C.D. Dumitru, M. Shimizu, R. Bichi, S. Zupo, E. Noch, H. Aldler, S. Rattan, M. Keating, K. Rai, *et al.* Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia Proc. Natl. Acad. Sci. USA, 99 (2002), pp. 15524-15529
5. A. Kozomara, S. Griffiths-Jones miRBase: integrating microRNA annotation and deep-sequencing data Nucleic Acids Res., 39 (2011), pp. D152-D157
6. M. Lindow, S. Kauppinen Discovering the first micro RNA-targeted drug J. Cell Biol., 199 (2012), pp. 407-412
7. A. Fire, S. Xu, M.K. Montgomery, S.A. Kostas, S.E. Driver, C.C. MelloPotent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans Nature, 391 (1998), pp. 806-811
8. M.K. Montgomery RNA interference: unraveling a mystery Nat. Struct. Mol. Biol., 13 (2006), pp. 1039-1041
9. M.R. Lares, J.J. Rossi, D.L. Ouellet RNAi and small interfering RNAs in human disease therapeutic applicationsTrends Biotechnol., 28 (2010), pp. 570-579

10. P. Hydbring, G. Badalian-VeryClinical applications of micro RNAs F1000 Res., 2 (2013), p. 136
11. V.N. Kim, J. Han, M.C. Siomi Biogenesis of small RNAs in animals Nat. Rev. Mol. Cell Biol., 10 (2009), pp. 126-139
12. M.J. Axtell, J.O. Westholm, E.C. LaiVive la différence: biogenesis and evolution of micro RNAs in plants and animals Genome Biol., 12 (2011), p. 221
13. V. AmbrosThe functions of animal micro RNAs Nature, 431 (2004), pp. 350-355
14. G. Meister, T. Tuschl Mechanisms of gene silencing by double-stranded RNA Nature, 431 (2004), pp. 343-349
15. S.M. Hammond, E. Bernstein, D. Beach, G.J. Hannon An RNA-directed nuclease mediates post-transcriptional gene silencing in Drosophila cells Nature, 404 (2000), pp. 293-296
16. J. Wang, Z. Lu, M.G. Wientjes, J.L.-S. Au Delivery of siRNA therapeutics: barriers and carriers AAPS J., 12 (2010), pp. 492-503
17. A.J. Stevens, J.J. Jensen, K. Wyller, P.C. Kilgore, S. Chatterjee, M.L. Rohrbaugh The role of public-sector research in the discovery of drugs and vaccines N. Engl. J. Med., 364 (2011), pp. 535-541
18. G.S. McMillan, F. Narin, D.L. Deeds An analysis of the critical role of public science in innovation: the case of biotechnology Res. Policy, 29 (2000), pp. 1-8
19. T. Laitala-Leinonen Update on the development of micro RNA and siRNA molecules as regulators of cell physiology Recent Pat. DNA Gene Seq., 4 (2010), pp. 113-121
20. E. van Rooij, A.L. Purcell, A.A. LevinDeveloping micro RNA therapeutics Circ. Res., 110 (2012), pp. 496-507
21. B.W. McLeod, M.L. Hayman, A.L. Purcell, J.S. Marcus, E. VeitenheimerThe 'real world' utility of miRNA patents: lessons learned from expressed sequence tagsNat. Biotechnol., 29 (2011), pp. 129-133
22. Li L, Wang L, Li L, *et al.*, Activation of p53 by SIRT1 inhibition enhances elimination of CML leukemia stem cells in combination with imatinib. Cancer Cell. 2012;21(2):266-281.
23. Peterson LF, Lo MC, Liu Y, *et al*., Induction of p53 suppresses chronic myeloid leukemia. Leuk Lymphoma. 2017;58(9):1-14.
24. Abraham SA, Hopcroft LE, Carrick E, *et al*., Dual targeting of p53 and c-MYC selectively eliminates leukaemic stem cells. Nature. 2016;534(7607):341-346.
25. Kesarwani M, Kincaid Z, Gomaa A, *et al.*, Targeting c-FOS and DUSP1 abrogates intrinsic resistance to tyrosine-kinase inhibitor therapy in BCR-ABL-induced leukemia. Nat Med. 2017;23(4):472-482.

How to cite this article:

Akash Pandey, Priyanka Singh and Kumud Malhotra. (2025). Identification of potential therapeutic targets for the development of novel treatment strategies in disease management*. Int J Recent Sci Res*.16(01), pp.061-068.

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