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Viruses as Anticancer Drugs: A Detailed Review

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Abstract**: Viruses are nature's nanoparticles, a vast untapped bio-resource. Oncolytic viruses is a new class of anticancer drugs which have advantages of selective replication in tumor cells, delivery of multiple eukaryotic transgene payloads, induction of immunogenic cell death and promotion of antitumor immunity. It is a tolerable safety therapy. Four oncolytic virus have been approved for the treatment of cancer globally. Talimogenelaherparepvec(T-VEC)istheonlywidelyusedtherapy.T-VECisused for treatmentofrecurrentmelanoma.[1] Oncolytic viruses are mutated such that they can be used as anticancer drugs in cancer therapy. They attack on selective tumor cells and destroy them without harming non-cancerous cells. With the help of virus-engineering strategies they are developed specifically for neoplastic tissues. Noninvasive pharmacokinetic monitoring is facilitated by engineering marker genes into the viral genome. [2] Oncolytic viruses are a class of therapeutic agents which give anti-tumor action by either selective tumor killing or induction of systemic anti-tumor immunity. Specific mutated viruses has been developed as oncolytic agents. Mechanism of action is likely dependent on viral replication within transformed cells, induction of primary cell death, interaction with tumor cell antiviral elements and initiation of innate and adaptive anti-tumor immunity. [3]We are going to see a brief review on the following topic in this article.

Keywords: Virus ,Anticancer ,Therapy ,Immunity , Nanoparticle

I. INTRODUCTION

A. *History*

In early beginning of 1900s, observations of viral infections causing tumor regression sparked interest in exploiting viruses for cancer treatment. [4] Initial experiments in between 1920-1950s, scientists tested various viruses including influenza and vaccinia against cancer cells in vitro and in animal models. [5] The first clinical trial held in between 1950-1960s, Oncolytic viruses were administered to cancer patients, showing promise but also limitations due to safety concerns and inconsistent results. [6] In between 1970-1980s, advances in genetic engineering enabled scientists to modify viruses to enhance their cancer selectivity and safety. In 1990s, Herpes Simplex Virus (HSV) was created. Researchers created HSV mutants with improved cancer killing properties leading to the development of talimogenelaherparepvec (T-VEC) approved by FDA in 2015. [7] Since 2000, researchers are exploring various mutated viruses including adenovirus, reovirus and coxsackievirus for their anticancer potential. Scientists are investigating combining oncolytic viruses with other cancer treatments such as immunotherapy and chemotherapy to enhance their effectiveness. [8]

B. *Advantages-*

1) *Targetedtherapy:*Viralvectorscanbeengineeredtoselectivelytargetcancercells,reducingtoxicityto healthy cells. [9]
2) *Cancercelllysis:*Oncolyticvirusescancausedirectlysisofcancercells,leadingtotumorregression. [10]
3) *Immune system activation:* Viral infection can stimulate anti-tumor immunity, leading to long-term cancer control. [11]
4) *Low toxicity:* Viral vectors can be designed to have minimal side effects, reducing harm to healthy cells.[12]
5) *Potentialforcombinationtherapy:*Oncolyticvirusescanbecombinedwithothercancertreatmentsfor enhanced effectiveness. [13]
6) *Tumor-specificreplication:*Somevirusescanreplicateselectivelyincancercells,amplifyingantitumor effects. [14]
7) *Systemicdelivery:*Viralvectorscanbeadministeredsystematicallyreachingdistanttumorsites. [15]
8) *Potential for personalized medicine:* Viral vectors can be trailored to individual patients of specific cancer types and genetic profiles. [16]

C. *Disadvantages*

1) *Costeffective:*Viralcancertherapiesmaybemorecosteffectivethantraditionaltreatments.
2) *Viralresistance:*Cancercellsmaydevelopresistancetotheviralvector,reducingitsantitumoreffect.
3) *Tumorheterogeneity:*Viralvectorsmaynoteffectivelytargetallcancercellswithinatumor.
4) *Deliverychallenges:*Deliveringviralvectorstodistanttumorsitescanbedifficult.
5) *Scalability:*Largescaleproductionofviralvectorscanbechallenging.

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6) *Regulatoryhurdles:*Strictregulationsgovernthedevelopmentandapprovalofviralanticancerdrugs.
7) *Publicperception:*Concernsaboutusingvirusesasdrugsmayeffectpublicacceptance.
8) *Potentialformutation:*viralvectorscanmutate,potentiallyleadingtounintendedconsequences. [17]

D. Ideal characteristics-

1) *Tumorspecificity:*Selectivelytargetandinfectcancercells,sparinghealthycells.
2) *Highreplicationefficiency:*Efficientlyreplicatewithincancercells,amplifyingantitumoreffects.
3) *Strongimmunestimulation:*Stimulatearobustantitumorimmuneresponse.
4) *Lowtoxicity:*Minimizeharmtohealthycellsandtissues.
5) *Stabilityandconsistency:*Maintainpotencyandconsistencythroughoutproductionandstorage.
6) *Flexibility:*Canbeengineeredtoexpressvarioustherapeuticgenesorproteins.
7) *Resistancetoneutralization:*Resistneutralizationbytheimmunesystem.
8) *Geneticstability:*maintaingeneticstabilitythroughoutreplicationandtransmission.
9) *Ability:*totargetcancerstemcells
10) *Costeffective:*Offeracosteffectivetreatmentoption.
11) *Non-pathogenic:*Donotcausediseaseinhealthyindividuals. [18]

E. Importance

Viruses havebeen harnessed as a novel class of anticancer agents, leveraging their inherent ability to selectively infect and kill cancer cells while sparing healthy tissues. [19] This innovative approach known as oncolytic therapy has gained significant attention in recent years due to its potential to overcome the limitations of traditional cancer treatments. [10] By exploiting the unique characteristics of viruses such as their ability to target specific cell types and stimulate antitumor immunity, researchers have developed a range of viral vectors with potent anticancer activity. [11]

II. MECHANISMACTION

Viralanticancerdrugsworkthroughvariousmechanisms,including:

A. SelectiveInfection

Virusesselectivelyinfectcancercells,sparinghealthytissues

B. ImmuneStimulation

Virusesstimulateantitumorimmunityenhancingcancercellkilling

C. Cancercelllysis

Virusescausedirectlysisofcancercells,reducingtumorburden.

D. AntitumorImmuneResponse

Thereleasedtumorantigensstimulateanimmuneresponseagainstcancer.

E. TumorMicroenvironmentModulation

Oncolyticvirusescanalterthetumormicroenvironmentmakingitmoreconducivetoimmuneattack.

F. DirectCellKilling

Someoncolytivvirusescandirectlykillcancercellsthroughapoptosisornecrosis.

G. Anti-AngiogenicEffects

Someoncolyticvirusescaninhibittumorangiogenesisreducingbloodsupplytotumor.

H. ImmunogenicCellDeath

Oncolyticvirusescaninduceimmunogeniccelldeathenhancingantitumorimmunity.[10,11,19]

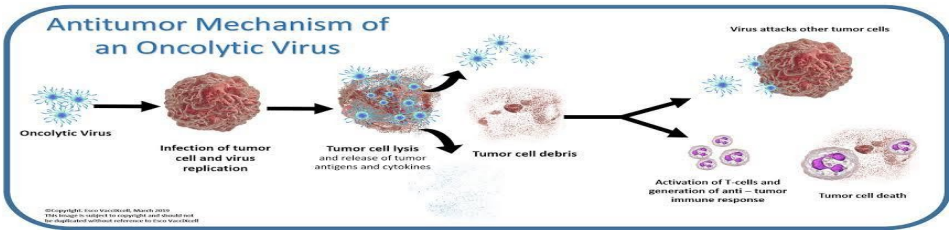


Fig.1

III. FUTURE DIRECTIONS

A. CombinationTherapies

Combiningviralanticancerdrugswithothertreatmentstoenhanceefficacy.

B. PersonalizedMedicine

Trailoringviralvectorstoindividualpatientspecificcancertypesandgeneticprofiles.

C. OvercomingResistance

Developingstrategiestoovercomeviralresistanceandensurelongtermefficacy.[10,11,19]

IV. TYPES

A. HerpesSimplexVirus(HSV)

Engineeredtoselectivelyinfectandkillcancercells,whilesparinghealthytissues.

B. Adenovirus(Ad)

Modifiedtotargetspecificcancercellsandstimulateantitumorimmunity.

C. Reovirus(Reo)

Naturallyinfectsandkillscancercells,withminimalharmtohealthycells.

D. VacciniaVirus (VV)

Usedasavectortodelivertherapeuticgenestocancercells.

E. NewcastleDiseaseVirus(NDV)

Stimulateantitumorimmunityandselectivelykillscancercells.

F. MeaslesVirus (MV)

Engineeredtotargetandkillcancercellswithpotentialforcombinationtherapies.

G. VesicularStomatitisVirus(VSV)

Rapidlyreplicatesinandkillscancercellswithminimalharmtohealthycells.

H. MarabaVirus (MV)

A rhabdovirus with potential for cancer treatment due to its ability to selectively infect and kill cancer cells.

I. SenecaValleyVirus(SVV)

Demonstratesantitumoractivityandpotentialforcombinationtherapies.

J. Coxsackievirus(CVB)

Showspromiseasanoncolyticvirus,selectivelyinfectingandkillingcancercells.[19,20,21]

V. APPLICATIONS

A. OncolyticVirotherapy

Virusesselectivelyinfectandkillcancercellsreducingtumorburden.

B. GeneTherapy

Virusesdelivertherapeuticgenestocancercells,promotingantitumoreffects.

C. Immunotherapy

Virusesstimulateantitumorimmunityenhancingcancercellkilling.

D. *CombinationTherapies*

Virusesarecombinedwithothercancertreatments,suchaschemotherapyorradiation,toenhance efficacy.

E. TargetedTherapy

Virusesselectivelytargetspecificcancercellsorpathways,reducingharmtohealthycells.

F. CancerStemCellTherapy

Virusestargetandeliminatecancerstemcells,reducingrecurrencerisk.

G. LymphomaTherapy

Virusesshowpromiseintreatinglymphoma,atypeofbloodcancer.[20]

H. SolidTumorTreatment

Virusesarebeingexploredfortreatingsolidtumors,suchasbreast,lungandcolorectalcancer.

I. PediatricCancerTreatment

Viruses offer potential for treating childhood cancers such as neuroblastoma and rhabdomyosarcoma. [21]

J. PersonalizedMedicine

Virusescanbetailoredtoindividualpatientswithspecificcancertypesandgeneticprofiles.

VI. DRUGS ELECTION CRITERIA

A. TumorSpecificity

Selectivelytargetsandkillscancercells,sparinghealthytissues.

B. OncolyticPotency

Effectivelykillscancercellsthoughoncolysis.

C. ImmuneStimulation

Stimulatesantitumorimmunity,enhancingcancercellkilling.

D. CancerStemCellTargeting

Targetsandeliminatescancerstemcells,reducingrecurrencerisk.

E. SafetyProfile :

Demonstratesminimaltoxicityandsideeffects.

F. DeliveryEfficiency

Canbeefficientlydeliveredtotumorsites.

G. GeneticStability

Maintainsgeneticstabilitythroughoutreplicationandtransmission.

H. Scalability

Canbeproducedinlargequantitiesforclinical use.

I. SynergyWithOtherTherapies

Enhanceseffectivenesswhencombinedwithothercancertreatments.

J. RegulatoryApproval

Meetsregulatoryrequirementsforclinicaluse. [22]

VII. COMPOSITION

A. Genome

Consistsofgeneticmaterial(DNA\RNA)encodingviralproteins.

B. Capsid

Proteinshellsurroundingthegenome,providingstructuralsupport.

C. Envelope

Lipidmembranesurroundingthecapsid.

D. Viralproteins

Performvariousfunction,suchasreplication,transcriptionandimmuneevasion.

E. Transgenes

Additionalgeneticmaterialinsertedintotheviralgenomefortherapeuticpurpose.

F. Promoters

Regulatoryelementscontrollingtransgeneexpression.

G. Oncolyticgenes

Genesencodingproteinsthatselectivelykillcancercells.

H. Immunestimulatorygenes

Proteinsrecognizedbytheimmunesystemastumorspecific.

I. Conditionallyreplicativeelements

Elementsallowingviralreplicationonlyincancercells.

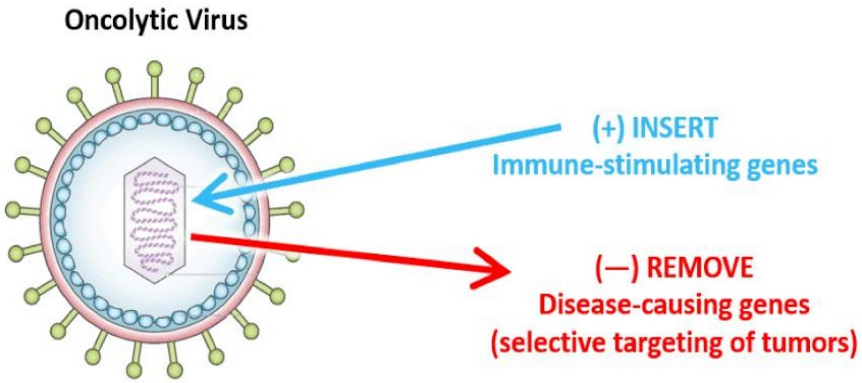


Fig. 2

VIII. MANUFACTURING

A. CellCultureBased Production
Growingcellsinbioreactorsandinfectingthemwith virus.
B. ViralVector Production
Usingplasmidsorothervectorstoproducethevirusincells.
C. BaculovirusBasedProduction
Usingbaculovirustoproducevirusininsectcells.
D. AdenovirusBasedProduction
Usingadenovirustoproducevirusinhumancells.
E. HerpesvirusBasedProduction
Usingherpesvirusestoproducevirusinhumancells.
F. Viruslikeparticle(VLP) production
ProducingVLPsthatmimicthevirusbutlackgenetic material.
G. MicrobialFermentation
Usingmicroorganismslikebacteriaoryeasttoproducevirus.
H. InsectCellBased Production
Usinginsectcellstoproducevirus.
I. MammalianCellBasedProduction
Usingmammaliancellstoproducevirus.
J. ClosedSystemProduction
Usingclosedsystemstoproducevirusminimizingcontaminationrisk.

IX. MAKING OF MODIFIED VIRUS

A. VectorConstruction
Creationoftheviralvectorincludinginsertionoftherapeuticgenes.
B. CellLine Development
Establishmentofacelllineforvirusproductionensuringconsistencyandscalability.
C. VirusProduction
Largescaleproductionoftheviralvectorusingcellcultureorothermethods.
D. Purification
Removalofimpuritiesandcontaminantsfromtheviralvectorensuringsafetyand efficacy.
E. ConcentrationAndFormulation
Concentrationandformulationoftheviralvectorintoafinalproduct.
F. QualityControl
Rigoroustestingforpurity,potencyand safety.
G. FillAnd Finish
Fillingandpackagingthefinalproductfordistribution.

H. RegulatoryCompliance

Adherencetoregulatoryguidelinesandstandardthroughouttheprocess.

X. EVALUATION

A. In-VitroCytotoxicityAssays

Assessingvirusmediatedkillingofcancercellsin culture.

B. In-VivoTumorModels

Evaluatingviruseffi cacyinanimalmodelsofcancer.

C. ApoptosisAssays

Measuringvirusinducedprogrammedcelldeathincancercells.

D. CellProliferationAssays

Assessingvirusimpactoncancercellgrowthanddivision.

E. ImmuneResponseEvaluation

Measuringvirusstimulatedimmuneresponsesagainstcancercells.

F. BiodistributionStudies

Trackingvirusdistributionandaccumulationintumorsandhealthytissues.

G. ToxicityAndSafetyAssessments

Evaluatingvirussideeffectsandsafetyinpreclinicalandclinicaltrials.

H. EfficacyAssessmentsInCombinationTherapies

Evaluatingviruseffi cacyincombinationwithothertreatments.

I. PharmacokineticAndPharmacodynamicStudies

Assessingvirusabsorption,distribution,metabolismandexcretion.

J. ClinicalTrials

Evaluatingvirussafetyandefficacyinhumancancerpatients.

XI. RESULT AND DISCUSSION

The purpose of clinical studies examining mutant viruses as anticancer medicines is to assess the safety and efficacy of these agents in identifying and eliminating cancer cells. For the purpose of figuring out how to include new therapies into conventional cancer treatments, these trials are essential.

A. TalimogeneLaherparepvec(T-Vec)

Thetreatmentofmelanomawiththisgeneticallyalteredherpessimplex virus is authorized.T-VEC showed a16%overallresponserate in patients with unresectable melanoma in akey trial that waspublished in theJournalof Clinical Oncology; some patients even experienced complete responses (Andtbacka.et.al.2015).

B. Oncovexgm-CS

This modified herpes simplex virus, an additional oncolytic virus, has demonstrated potential in melanoma clinical trials, resulting in immune activation and tumor shrinkage (Cohen et al., 2015). Reovirus, or Reolysin:-Numerous malignancies, including head and neck tumors, have been studied in relationto this naturally occurring virus. Reolysin has been shown to increase the effectiveness of chemotherapy and improve patient outcomes, according to a study published in Clinical Cancer Research (Gerritsen et al., 2014). [23]

C. Efficacy Outcomes

A lot of studies show improvements in survival rates and tumor shrinking. For instance, approximately 16% of patients in the T-VEC studies had lasting responses, and some of them had complete responses(Andtbacka.et.al.,2015).[24]

D. Safety Profile

These modified viruses are typically considered safe. The majority of side effects, such flu-like symptoms,aremildtomoderate.Therarityofseriousadverseeventsispositiveforcurrentandupcoming research

E. Combination Therapies

Oncolytic virus trials are also investigating the use of these drugs in conjunction with immune checkpoint inhibitors and other treatments. According to preliminary findings, these combinations may strengthen therapeutic benefits and improve patient outcomes (Cheng et al., 2020).

F. Regulatory Acceptance and Upcoming Trials

Some treatments, like T-VEC, have received regulatory approval as a result of the positive results of early trials. New mutant viruses and their potential in combination therapy are still being investigated by ongoing research. [25]

Clinical investigations show that mutant viruses offer a great deal of promise as anticancer medications, giving patients with a variety of tumors hope. To maximize their utilization and broaden their uses in oncology,ongoing research is crucial.

XII.MARKETED EXAMPLES

Brandname	Virusname	Mfg. company	Cost (per treatment)	Region of use	indiction
Imlygic	Talimogenelaherparepvec	Amgen Inc.(USA)	$65000	USA	Melanoma
Oncorin	Adenovirus based	Shanghai Sunway Biotech Co. Ltd.(China)	$45000	China	Headandneck cancer
Reolysin	Reovirusbased	Oncolytics Biotech Inc.(Canada)	$30000	Canada	Ovarian
Rigvir	Picornavirus based	Latvian Biomedical Research and study centre(Latvia)	$20000	Latvia and Georgia	Melanoma
Theravir (G47Δ)	Herpisvirus based	Takara Bio Inc.(Japan)	$10000	Japan	Glioblastoma
CavatakA21	Coxsackievirus based	ViralyticsLtd.(Australia)	$20000	Australia	Melanoma
Vaxinia (JX-594)	Poxvirusbased	Jennerex Biotherapeutics Inc.(South Korea)	$30000	Southkorea	Livercancer

Table 1

XIII. CHALLENGES AND LIMITATIONS

Thereareanumberofdifficultiesandrestrictionsassociatedwithusingmutantvirusesasanticancer medications. Here are some important things to think about:

A. Safety Concerns

*1) Toxicity:*Oncolyticvirusescarrythepotentialtodamagenormal,healthycells,which could result in unforeseen side effects.

2) ImmuneResponse:Thevirusmaybeneutralizedbeforeithasachancetoinfectcancercellsiftheimmune system perceives the viral therapy as alien and launches a strong defense.

B. Efficacy

*1) TumorHeterogeneity:*Tumorscanexhibitavarietyoffeaturesduetotheirheterogeneity.Because of this variety, it may be challenging for a single viral therapy to eradicate every cancer cell present in a tumor.

2) Resistance:Overtime,cancercellsmaybecomeresistanttoviralinfectionorreplication,whichwould decrease the treatment's efficacy.

C. Delivery Challenges

1) *TargetingTumors:*Itcanbedifficulttoeffectivelytransportthevirustothetumor site, particularly if it is deep-seated or located in a complicated anatomical region.
2) *ViralSpread:*Maximizingtheeffectivenessoftreatmentrequiresthatthevirusspreadsefficientlywithinthe tumor and reaches every cancer cell. [26]

D. Regulatory and Ethical Concerns

1) *PermissionProcedure:*Creatingandreceivingregulatorypermissionfor viral treatments can be a drawn-out procedure that necessitates substantial preclinical and clinical research.
2) *EthicalConcerns:*Researchanddevelopmentmaybecomplicatedbyethicalconcernsabouttheuseof genetically modified organisms in humans.

E. Cost and Accessibility:

1) *HighCosts:*Thecreation,study,andmanufacturingofoncolyticvirusescanbe costly, which may restrict patient accessibility.
2) *LimitedAvailability:*Therearecurrentlyapprovedviraltherapiesforasmallnumberofmalignancies,and further research is required to increase the number of tumors that can be treated.

In conclusion, although mutant viruses have great potential as anticancer medications, there are a number of issuesandrestrictionsthatmustberesolvedtoguaranteetheirsafeandefficientapplicationinclinicalsettings. [27]

XIV. ADVANCES

Futuredevelopmentsforemployingmutantvirusesasanticancermedicationsareveryencouragingandcenter on a number of important areas, including:

A. Genetic Engineering

Toimprovetheselectivityandeffectivenessofoncolyticviruses,scientistsare investigating cutting-edge genetic editing methods. One example of this is creating viruses with precise targeting capabilities that spare healthy cells.

B. Personalized HealthCare

Thefocusoffuturetherapeuticsmaybeoncustomizingviraltherapiestothe tumor characteristics of specific patients. Viral therapies that are specifically tailored to the genetic and molecular characteristics of a patient's cancer can be developed for more successful treatment.

C. Improved Distribution Method

It is essential to develop more effective delivery strategies to guarantee thatthevirusessuccessfully infecttheirintendedtumors. Thiscouldentailenhancingthediffusionanduptakeof viral treatments through the use of nanoparticles or other cutting-edge methods. [28]

D. Comprehending The Immune Reaction

Finding out how the immune system engages with oncolytic virusescanhelpdeveloptacticsthatmaximizepositive effectswhileboostingtheimmunesystem'sdefensesagainstmalignancies.Thismaycontributetooptimizingthetherapeuticadvantagesofviraltreatments.

E. Regulatory Advancements

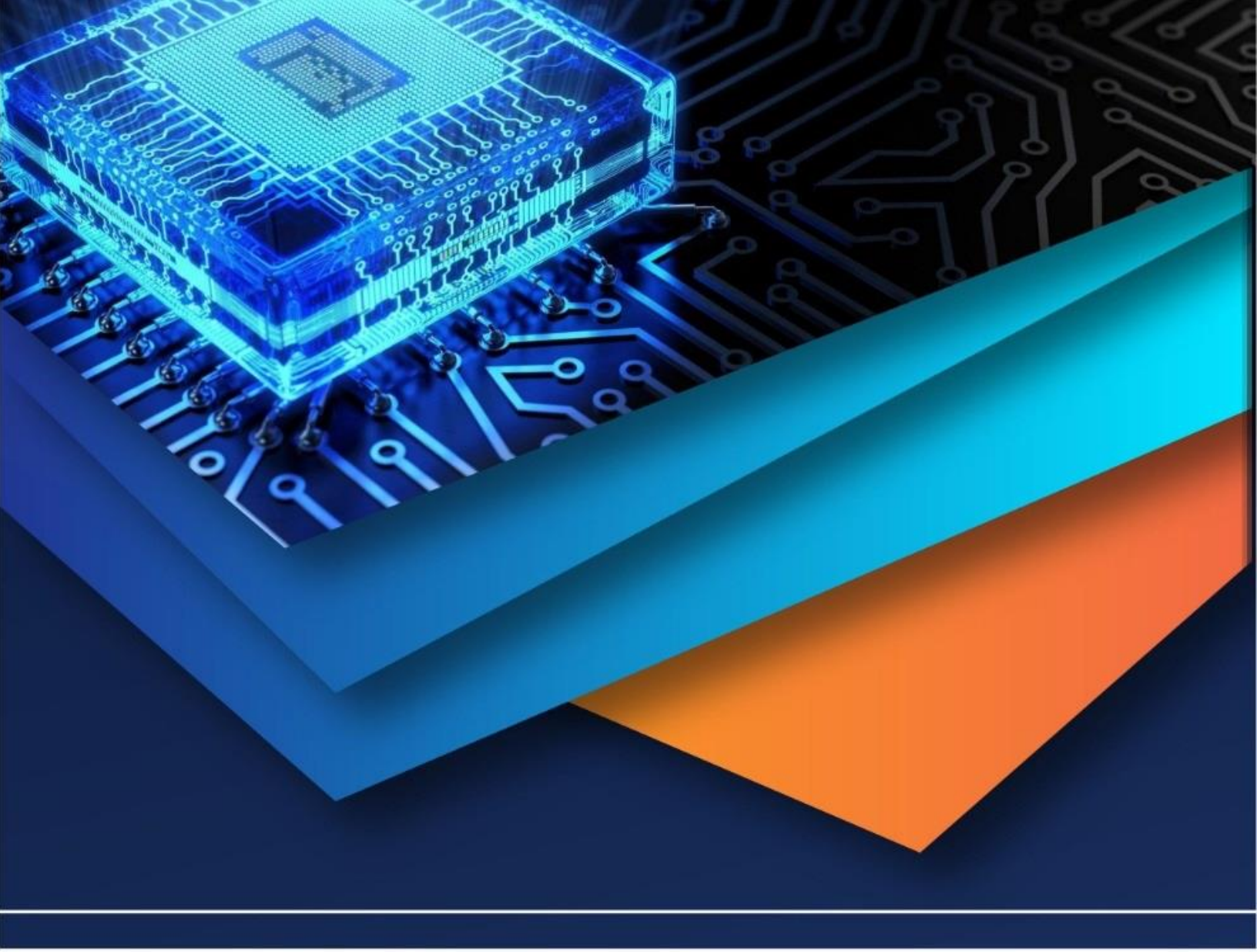
Asthefielddevelops,regulatoryframeworksmayadvanceinawaythat expedites the approval of potential viral medicines, giving patients speedier access.Insummary, the developmentofmutantviruses as anticancer medicationswillrevolvearound enhancing their efficacy,safety,andavailabilityviacreativeresearchandcombinationapproaches.Intheupcomingyears,this may result in cancer patients receiving more potent treatments. [29]

XV. CONCLUSION

Utilizing certain viruses' innate capacity to specifically infect and destroy cancer cells while inducing animmune response, mutated viruses as anticancer medications provide a novel approach to the treatment of cancer. Treatments that are more precise and efficient are coming from the continuous research in genetic engineering, combination therapy, and customized medicine. These treatments appear to have a good chance of becoming commonplace choices for cancer patients as long as clinical trials proceed. In summary, the future of mutated viruses in cancer therapy isbright,with ongoing advancements likely to yield significantbreakthroughs in the fight against cancer. [30]

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