



## **Organoids as a Form of Modern Day Silver Lining**

**S. Danish Kadir<sup>1\*</sup>**

<sup>1</sup>*Department of Pharmacy, Rajshahi University, Bangladesh.*

### **Author's contribution**

*The sole author designed, analyzed, interpreted and prepared the manuscript.*

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### **ABSTRACT**

Blood Cancer-in the shape of carcinogenesis, is worldwide recognized, as a recent time catastrophe. Its unique capability of sustaining its dormancy, vulnerabilities, of drug screening methodologies, and most importantly therapeutic resistance of tumour affected stem cells(due to the redundancy of CD-133+ cells against Radio therapeutic treatment procedure and existence of MDR-1, and ALDH-1 proteins in drug screening methodologies) [1] has transformed blood cancer, as hardly curable. To face this challenge; Organoids are figured out to be a possible solution. From a researcher's point of view organoids are generally 3D structured in (vivo) clusters of stem cell molecules [2], showcasing bio-active capabilities. However, the lower success rate of organoids, bespeaking its initial stages of preclinical level of studies. In addition, most of these models & their implications just only been limited to in (vivo) principles and various forms of cancer exemplifying; Blood lymphoma. Interestingly, some recent milestones of organoids in different research models on metastasis reflect the glimpses of hopes. At this present study, we have worked on organoids and their possible involvement in blood cancer. We have emphasized on organoid modelling both in (vivo) and in (vitro) cell culture, which are some excellent sources for cell analysis. Presently, we have established a model where a Nano-sized in (vitro-vivo) cell clustering of organoids with an MRI scanning technique been utilized to build a more precise and useful therapeutic tool. This innovative approach would help us to identify the tumours that will not respond to any conventional therapies. Also in our studies the organoids have shown active cellular level of immunomodulation, leading to a proper signal transduction. As a consequences, this revolutionary model creates opportunities for a better outcome in terms of diagnostics and therapeutics.

**Keywords:** Blood cancer; *in vivo-vitro* models; organoids; revolutionary model; diagnostics; immunomodulation.

## 1. INTRODUCTION:

From the preface of the eclipse of an unknown erstwhile to the dawns of the most advanced 21<sup>st</sup> century, Blood cancer has always been figured out to be an unbridled deterrent against the existence of human souls. Leukemia, Lymphoma, and Myeloma [3] are all of the three different existing forms of blood cancer, reflecting the various levels of its fatality and pathogenicity. Its higher percentage of its morbidity resembling the atrocious side of this havoc. According to some recent data interpretations, Blood cancer is being primarily termed as responsible for the deaths of almost a single living person within a span of every 9 minutes in USA in 2017 [4]. Previously utilized drug therapeutics and treatment modalities such as; Surgery, Chemotherapy, Radiotherapy and recently experimented immune therapeutics showing a class of high success rate by dwindling the death percentage by almost 70 percentiles. However, they are still unable to eradicate this apocalypse. The primary analytical reports symbolizing the main obstacles behind the treatment policies of blood cancer are:

- The inability to target and the supreme capability of the resistance of human stem cells against various types of cancerous medications.
- Lack of cancer epigenetics profiling and specificity suggesting the unfortunate aspects of its inability to treat tumor, even within the same origin and similar characteristics.
- Metastasis of cancer tumor cells paving a way for some research output on something effective and advanced, especially in blood cancer.
- The Non-specific nature of cancer symptoms and the problems associated with cancer diagnosis making it harder to treat.

**Example:** The current imaging tool PET-CT technique is still unable to predict the responses with reliable accuracy and not that much effective towards a more individualized treatment policies, urging on the necessity of innovative therapeutic solutions like; Organoids. That is why this proposed theory surrounding the active responses of organoids as an anti-oncogenic agent, has a huge potential to fulfill [5].

Nevertheless the lower success rate of organoids could be used as an obstruction against this proposed one, but here the issued researchology working on the whole aspect, is completely based on the liabilities of those upwardly discussed processes and an advancement of organoid theorem. Furtherly, the vulnerabilities of 2D cell cultures in terms of-

- The Inability to stimulate the micro-environment and organ specific functions [5]
- Lacking's of the proper genetic heterogeneity of original tumors. Indicating the soften corner in this route of analysis.

**Whereas, the activity of 3D *in vivo-vitro* model featuring the followings:**

- The effectiveness in both *in vivo* and *in vitro* counterparts and
- The performance of the assay techniques associated with a purpose to differentiation, diagnosis, and its usefulness *in vivo* self-proliferation and efficiency in the treatment of individually affected cancer cells [6]

From an additional point of view, MRI scanning techniques could be utilized as a trump card in a similar scenario. This Magnetic Resonance Imaging technique possessing, the ability to add a new dimension to the ongoing procedure has the ability to make the diagnosis and prognosis process a far more precise and effective in nature. Therefore, the organoids could easily be available to resolve the missing puzzle.

## 2. MATERIALS AND METHODS

Before coming to the research procedure, we require to put our emphasis on necessary basics, materials, and their rationale, which has inspired us to go through the development of our blood cancer research methods.

## 3. CHALLENGES ASSOCIATED WITH BLOOD CANCER

The obstacles following the treatment of various blood cancer are:

- While targeting there are abundance of hugely successful techniques out there to

figure out the possible cancer stem cells and most of them are precise in nature. However, there are still some rare occasions where the diagnose outcome is not accurate enough but the outcome is still fatal and could easily lead to a deaths.

- Drug resistance properties of stem cells
- Lack of cancer epigenetic profiling & specificity of existing Epi-drugs.
- Unavailability of effective biomarkers in blood cancer.
- Limitations of conventional chemotherapeutic agents.
- Metastasis posing a huge obstacle to the treatment of cancer.

#### 4. MECHANISM OF BLOOD CANCER

The stem cells originating from the bone marrow leading to the development of Hematopoiesis [7]. Usually, stem cell molecules are constantly divided to produce a new cell [8]. Whereas, in blood cancer it may sometimes go through a passage of unnatural cell division, anemia or the signal transduction pathway gets severely damaged. AS a result, the differentiation, transduction, and repair mechanism gets completely hampered, as well as the cell proliferation process [9].

The greatest asset of these models is to reflect not just only on the ability to handle the metabolic changes [6], but also to help to express the genes. As a possible consequences, Normal progenitor cells can easily lead to the repairmen and regeneration after the possible damages.

#### 5. ORGANOID'S OVERCOME THERAPEUTIC RESISTANCE

CSC possessing the ability to exert resistant to chemotherapeutic & radio therapeutic actions, as well as quite effective against drug screening methodologies. A merely portion of cancer stem cells. A merely portion of cancer stem cells [10] after a process of therapeutics can survive & lead to the promotion of cancer relapse and resistance. The regulated targeting pathways can lead to the sustainability & proliferation plays a crucial role in drug resistance.

#### 6. WHY NANO-MRI SCANNER

MRI Scanner is an ideal media to diagnose. Magnetic Resonance Imaging technique uses strong magnetic field gradients and in here, The Nano-ranged wave technology to generate the in (vivo) images of the human body on different

slices like; Sagittal, Axial, Limbic [11] to get an ideal diagnosing outcome.

It is advantageous to use an MRI scanner, as it does not have any ionizing radiation technology leading to toxicity. Before going through the MRI scanning process, the subject is injected with the dye. Aftermath, Nano ranged estimation aids us to observe and diagnose.

The greatest asset of this type of MRI scanners is the ability to get a gradual improvisation, as the more

Advanced generation reflects on the shorter passage of scanning period.

Though it usually takes around (30-60) minutes [12] to make a complete scan, here it has taken a figure somewhere close to (10-15) minutes.

[NOTE: The ideal 3D organoid cell culture having Lamnin riched Matrigel, Growth factors & small cell inhibitors] [6]

In additional sense,

- It would aid the diagnosis quite accurately.
- Greater application of the media.
- It helps in the 3D culture of organoids

The liabilities of some of the orthodox therapeutic methodologies could pave the way for further development of the therapeutics from diagnosis to treatment procedure. That's why we have proposed a model to utilize nanotechnology in MRI scanners in order to-

- Reduce the time required for the complete diagnosis.
- To perform a complete diagnosis procedure far more accurately.
- Nano range technology in MRI scanners would also aid us to eradicate the challenges associated with over diagnosis, because of the in details and precise analysis of the cancer affected stem cells [13] Generally, in MRI scanners the range of the wavelength is approximately around millimeter, but in our proposed case study, we use a wavelength of ( $10^{-9}$ ) or nm. This proposed mechanism will help us to accurately figure out far more accurately and effectively. However it will maintain all the others principles of an ordinary MRI machine even the identification procedure is also maintained similar to previous times MRI machines.

**Table 1. Differences between normal stem cell & cancer stem cell [14]:**

<b>Normal stem cell:</b>	<b>Cancer stem cell:</b>
The self-renewal capacity of normal stem cell is highly regulated and limited to a definite extent.	Cancer stem cells self-renewal capability is quite indefinite & dysregulated.
The karyotype is quite normal in nature.	Karyotype for cancer stem cell shows greater number of abnormality.
STEM cell shows organogenic characteristics.	CSC reflects a sign of tumorigenic capacity at a significant portion.
Quiescent in nature	Mitotically less active
SC has been supported by niche providing homeostasis maintenance.	CSC may involve deregulation or alteration of the niche by dominant proliferation promoting signals.
A contrary scenario been observed in case of normal stem cell	CSC shows completely different characteristics in the cell adherence in both serum free (CSC cannot survive) and serum based growth factor like environments (can easily sustain its existence).

## 7. GENERAL OVERVIEW

Self-developing capability among inherently affected stem cells is a renowned assumption among scientists and has initiated researchers to develop a 3D in (vivo-vitro) cell culture models from primary tissues of bone marrow [6]. Both in (vivo-vitro) models of organoids representing a more reliable and idealistic response compared to usual cell lines, outlasting recapitulation and manipulation capacity [6].

## 8. RESEARCH PROCEDURE

In recent times, the success of both in (vivo) & in vitro organoid cell culture & its wonderful supremacy, while showing mimicry, provides the characteristics of heterogeneity [6].

### CULTURE SYSTEM OF BLOOD CANCER:

This proposed research model is composed of the following components [5]:

- Matrigel Matrix.
- ECM extract.
- Advanced DMEM/F12.
- Gluta Max.
- HEPES.
- Noggin.
- R-Spondin-1[15].
- Nicotinamide.
- A-83-01.
- Y27632.
- Gremlin 1[15].
- Darbepoetin-alpha.

- Peginesatide.
- Romiplostim.
- WNT pathway inhibitor.
- Hedgehog pathway inhibitor.
- Farnesyl transferase inhibitor.
- Aurora A kinase inhibitor.
- Histone deacetylase.
- HSP90.
- Proteasome inhibitors.
- Nicotinamide.

It is to be noted that here the existence of ECM substituents is the differentiating constituents between 2D & 3D organoid cell culture [6], where the advanced DMEM/F12 is being utilized as the ideal cell culture media.

Name of the constituents utilized in the formulation of advanced DMEM/F-12[16]:

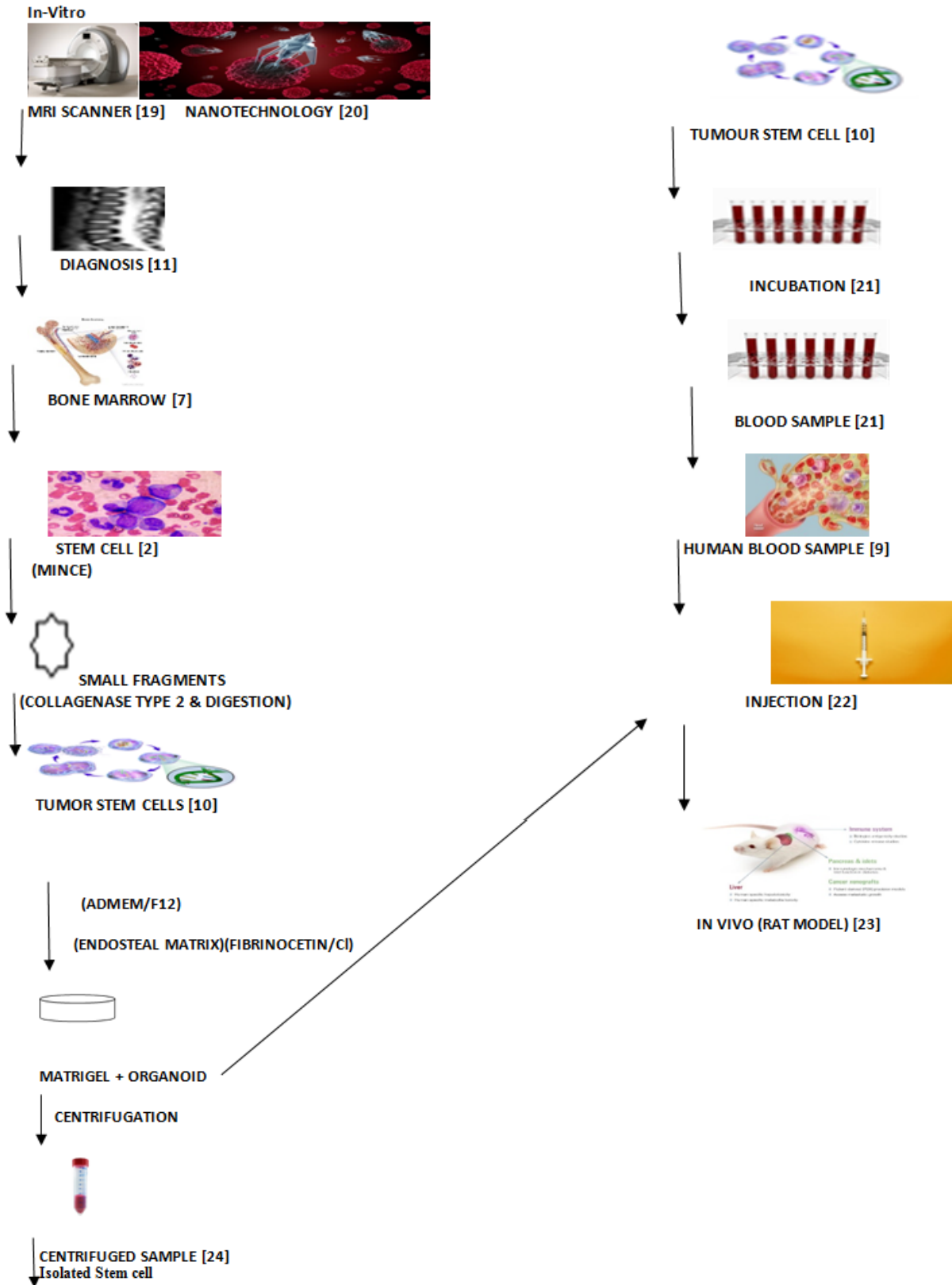
- Glucose
- Non-essential amino acids
- Sodium pyruvate
- Phenol red

### WHY ADVANCED DMEM/F-12 IS UNIQUE:

The reasons to be bolded behind the usage of Advanced DMEM/F-12 are [17]:

- Inexistence of L-glutamine
- HEPES are not used.
- Reduced (FBS) supplementation compared to classics, where reduction occurred by almost (50-60) percentiles [18]

**Our modified proposed organoid model in the treatment of blood cancer:**



**Fig. 1. *In-vivo* establishment of Blood Cancer model**

## 9. *In vivo* SCENARIO

Transgenic mice models are implemented to resume the experiment in (vivo) analytical condition [23]. Here, the mutated genes of human blood cancer [21] are induced to the growth of blood cancer affected cells. MRI analytical technique is being widely designed for the observational studies [19].

[NOTE: In the research experiment;

- There are around 60 transgenic mouse. Divided into 4 different groups consisting of 15 transgenic mice.
- All of the animals whom are sampled, at the ambient room condition and reared at a dark & isolated room condition.
- Almost half of the total experimental are males & half of the other portion are females.
- The whole study is done at a total time expenditure of 6 months period and all the animals are experimented quite regularly.

- Among all of the experimented animals, at least (90-95) percent of them requires to be observed and requires show optimistic outcome for a successful experimentation

## 10. *In vitro* SCENARIO

The economically balanced, genetically manipulated, and flexibly molded in (vitro) model shows a series of active phenotypic responses. Proving its worth as a recognized assay [22].

Enzymatic expression in blood cancer is a good option to target [25]. That's why the inhibitors of those channels and their enzymatic activities of the protein level inhibitors been activated. Utilization of Nano wavelength for the purpose of analyzing the targets to establish a proper study model, possessing a superior accuracy and greater efficiency to detect deep lying tumors with relatively ease [20].

**Table 2. Growth factors applied in organoid cell culture**

Name	Function	Structure/source/components
R-SPONDIN-01	•Facilitation of the growth of metastasis[6]	•Chromosome •2cysteine ring •1 thrombospondin type 1 domain
NOGGIN	•Promotion of bone metastasis of some cancers & association with tumorigenesis of primary bone malignancies [6]	•HGNC:HGNC:7866
FLT3	•Formation of fms regulated tyrosine kinase 3 •Signal transduction [26]	•HGNC:HGNC:3765 [26]
DARBEPOETIN ALPHA	Stimulates •erythropoiesis •Anemia	•C815H1317N233O241S5
NICOTINAMIDE	•A Vitamin PP is a nutrient required for long term organoid culture	•C6H6N2O [27] •Nicotinic acid or 3 cyanopyridine
PEGINESATIDE	Stimulates •Anemia •It mimics the structure of Erythropoietin & promotes the RBC development	•C231H350N62O58S6[C2H4O] <sub>n</sub>
ROMIPLOSTIM	A hormone that regulates platelet production	• C2634H4080N722O790S18 [28] •Analogue of thrombopoietin

**Table 3. Inhibitors applied in organoid cell culture**

<b>Name</b>	<b>Function</b>	<b>Structure/source/components</b>
GREMLIN 1	•Inhibition of predominant BMP2& BMP4 in limb buds allows the transcriptional upregulation of FGF'S & SHH ligands.	•Embryonic fibroblast •Furin like domain •184 Amino acid glycoprotein
HISTONE DEACETYLASE INHIBITOR	•Inhibition of histone deacetylase	•2 classes: HDAC & HDI
AURORA A KINASE INHIBITOR	•Regulation of serine/threonine kinases •Anti-cancer agents	•encoding aurora A,B, & C.
FARNESYL TRANSFERASE INHIBITOR	•A preventive function	•A 4 Amino acid sequence at The carboxyl terminus of a RaS. (48KDa & 46KDa)
PROTEASOME INHIBITOR	•Blocks proteasomes	•Proteolytic site on the Eukaryotic cells
WNT PATHWAY INHIBITOR	•Promotion of cancer & progression of it [29]	•WNT ligand or receptors •3signaling pathways: canonical, noncanonical planar cell polarity,non-canonical WNT/calcium
A-83-01	• A transforming growth factor beta inhibitor suppresses the proliferation of organoids [6]	•C25H19N9S • HHI:Results of aberrant component of the Hedgehog signaling pathways. •3different classes; Shh, GLI, SMO [30]
Y27632	•Inhibition of Rho kinase [6] •Improves culture [6]	•C14H21N3O
HEDGEHOG PATHWAY INHIBITOR	•Inhibits the growth of cell [31] •Activates tissue repairmen and cell proliferation	•3FDA approved inhibitors: Vismodegib, Erismodegib, Smoothened •It's a kind of glycoproteins
MATRIGEL INHIBITOR	• Mimicry in vivo 2D & 3D environments •Improvement of the differentiation of both normal and transformed anchorage dependent epithelial cells	•Sarcoma cells
HSP 90 INHIBITOR	•Inhibits collagen I & ii • Inhibits Matrix metalloproteanase-3 to Reduce cell Metastasis	•3 types of Natural product geldanamycin (C29H40N2O9), radicicol(C18H17ClO6), 17AAG (C31H43N3O8).

Various types of blood cancer, their development, & the principle of present inhibitors:

**CLASSIFICATION OF BLOOD CANCER [32]:**

Blood cancer can easily be divided into the following way:

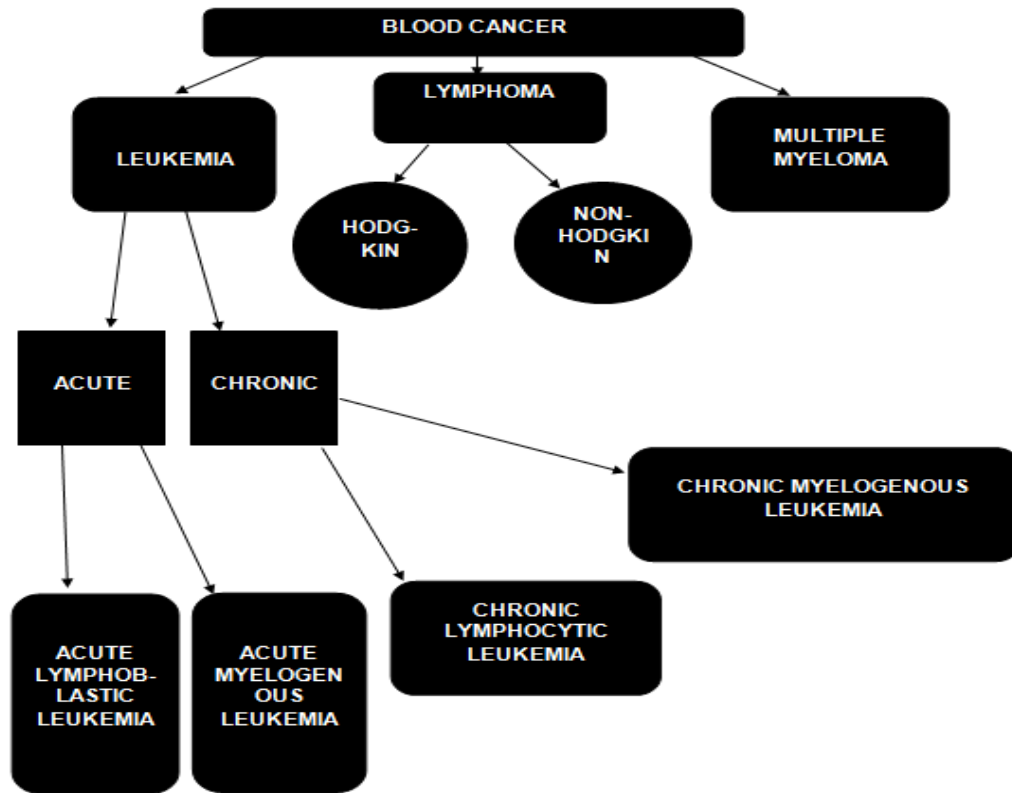


Fig. 2. Classification of blood cancer

**11. ACUTE LYMPHOBLASTIC LEUKEMIA:**

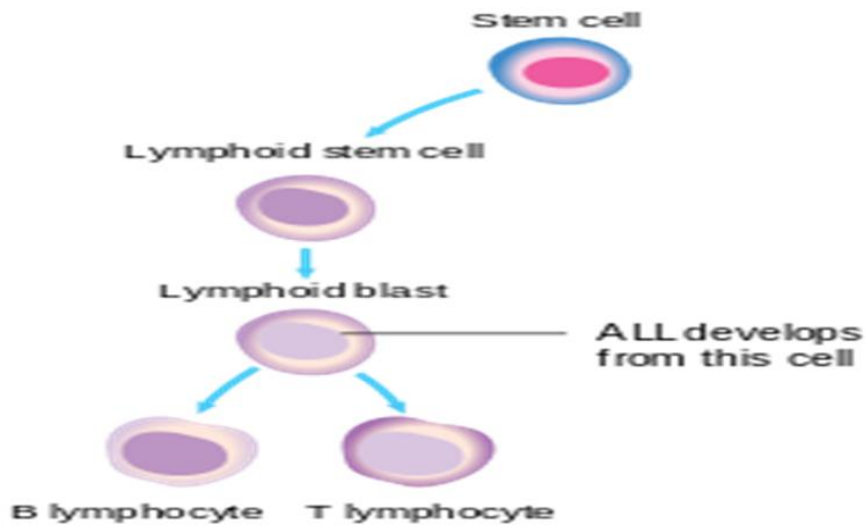
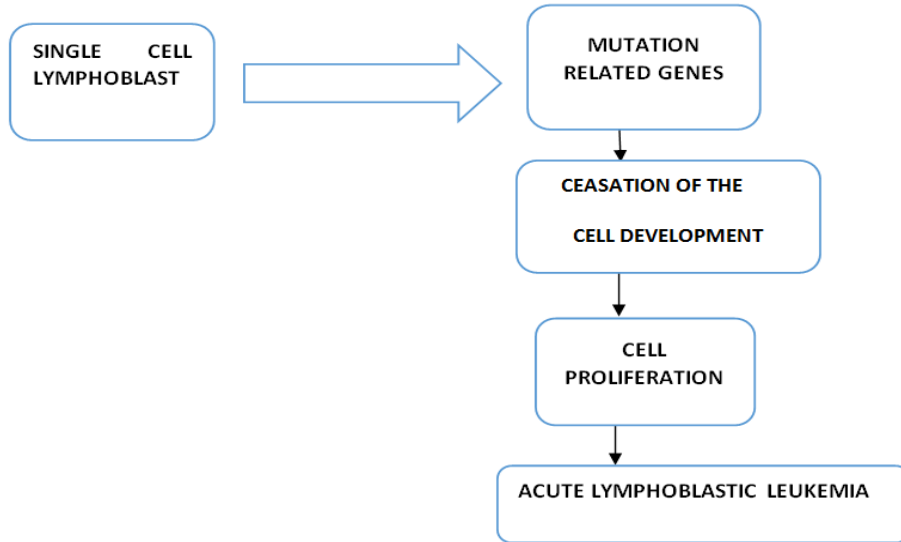


Fig. 3. Acute lymphoblastic leukemia [33]



**FORMATION OF ACUTE LYMPHOBLASTIC LEUKEMIA:**



**Fig. 4. Development of acute lymphoblastic leukemia**

**MECHANISM OF INHIBITORS:**

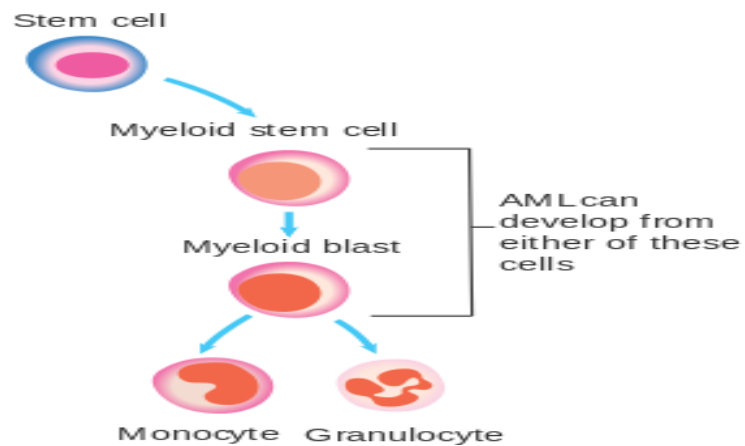
- Inhibits tyrosine kinase inhibitors.
- Activates proteins by signal transduction cascades.



[NOTE: Tyrosine kinase inhibitors ability to deprive Tyrosine kinase to access HSP 90]

**Fig. 5. Mechanism of inhibitors in acute lymphoblastic leukemia**

**12. ACUTE MYELOGENOUS LEUKEMIA**



**Fig. 6. Acute myelogenous leukemia [34]**

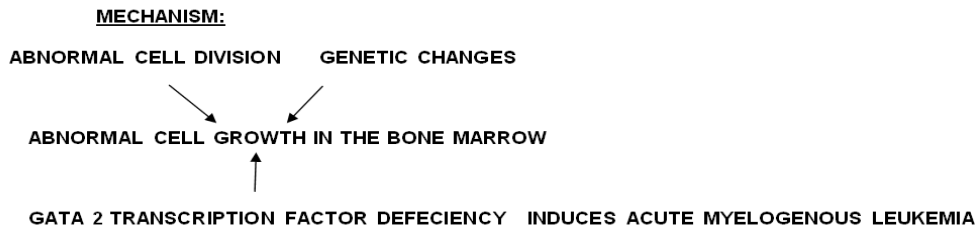


Fig. 7. Mechanism of the development of myelogenous leukemia

**INHIBITORS:**

- Histone deacetylase.
- Tyrosine kinase inhibitors.

**13. CHRONIC LYMPHOCYTIC LEUKEMIA**

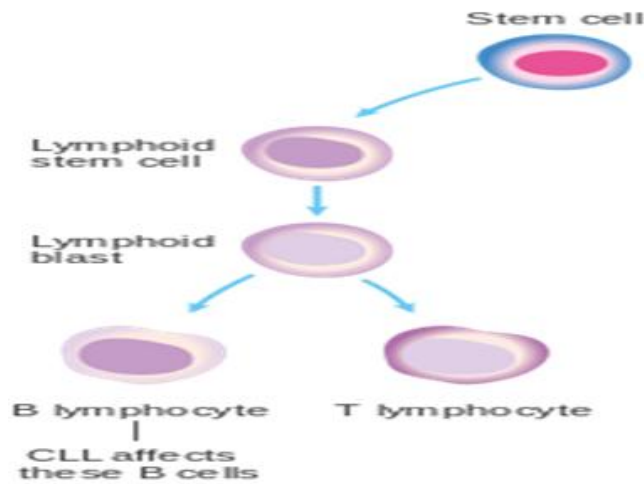


Fig. 8. Chronic Lymphocytic Leukemia [35]

Chronic Cancer results as the bone marrow produces a handful number of lymphocytes.

**REASONS:**

- Genetic mutations
- Epigenetic changes

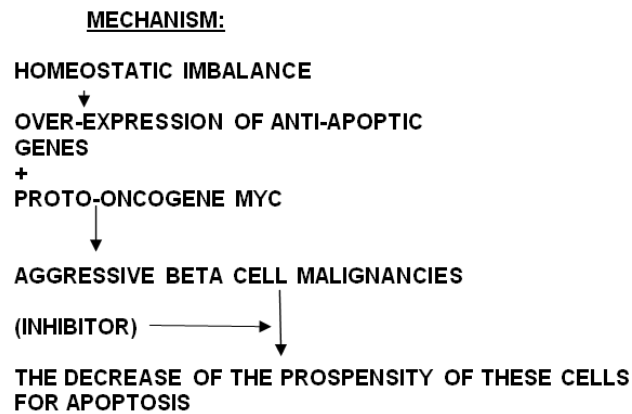


Fig. 9. Mechanism of inhibitors in chronic lymphocytic leukemia

**INHIBITORS:**

- BCL-2 inhibitor
- Bruton's tyrosine kinase inhibitor
- Phosphoinositide-3-kinase inhibitor

**14. CHRONIC MYELOGENOUS LEUKEMIA**

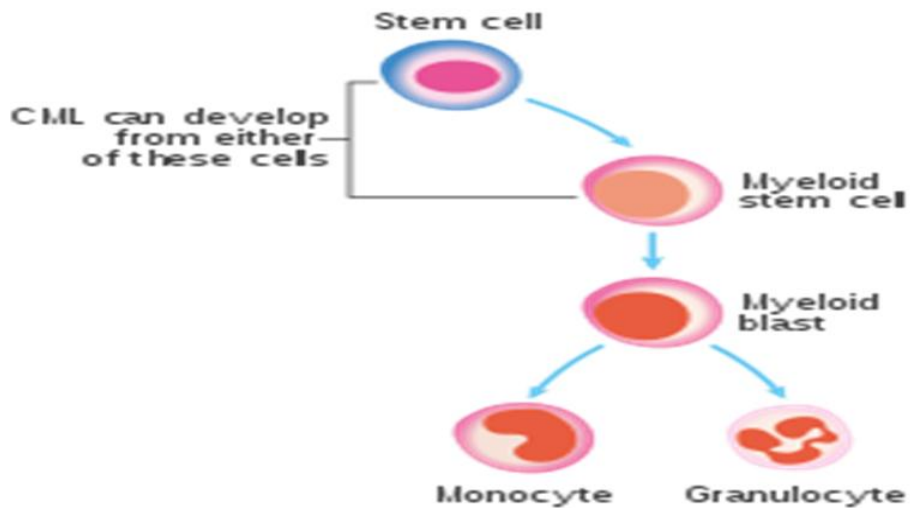


Fig. 10. Development of chronic myelogenous leukemia [36]

**MECHANISM:**

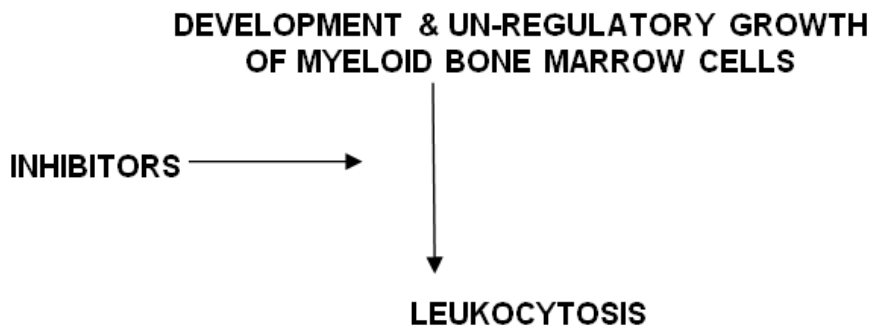


Fig. 11. Mechanism of inhibitors in leukocytosis [24]

**INHIBITORS:**

Tyrosine kinase inhibitors [36]

**15. LYMPHOMA**

2 types of Lymphoma. Hodgkin & Non-Hodgkin lymphoma.

**HODGKIN LYMPHOMA**

- Lack of CD surface antigens results in Hodgkin lymphoma [37].
- MOPP was initially used to treat Hodgkin lymphoma.

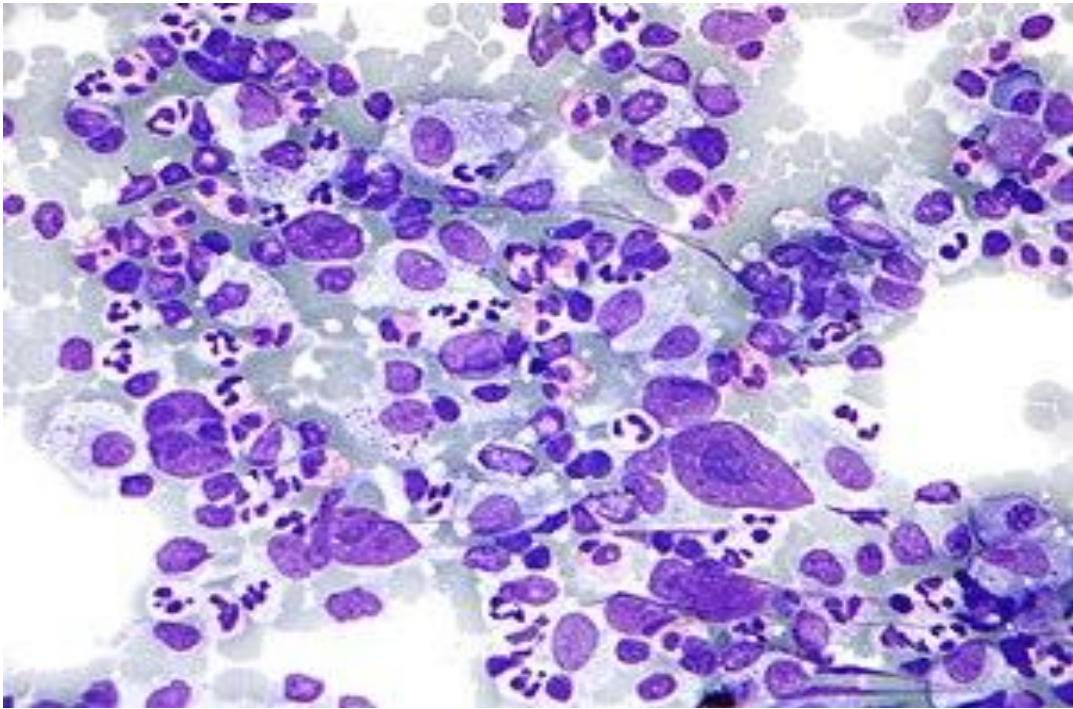


Fig. 12. Hodgkin lymphoma [38]

**NON-HODGKIN LYMPHOMA:**

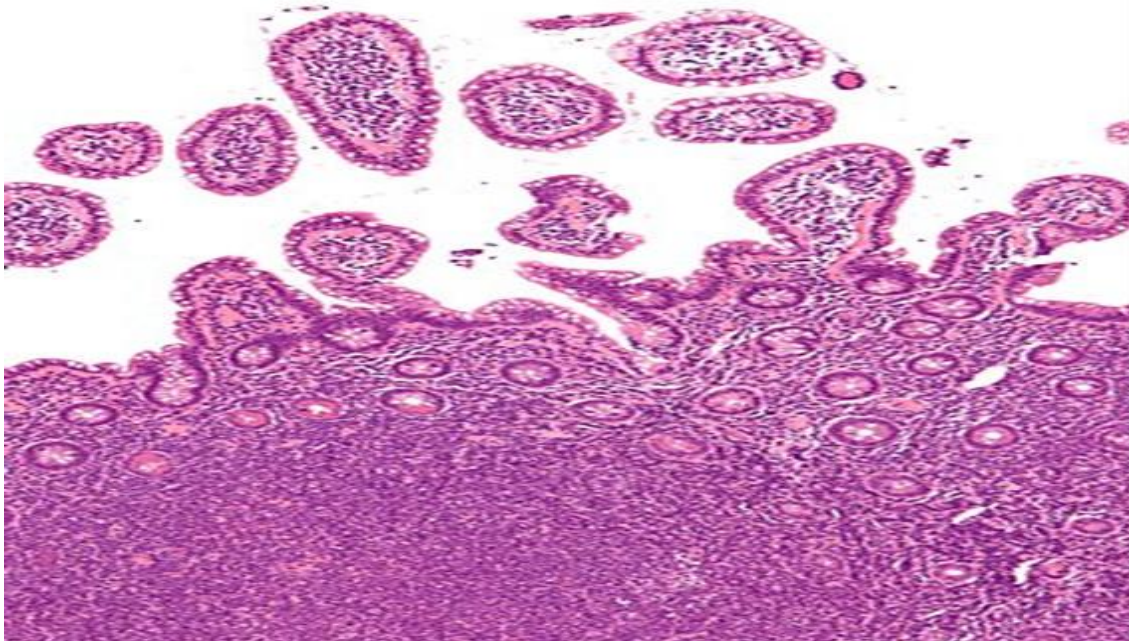


Fig. 13. Non-hodgkin lymphoma [37]

**INHIBITORS:**

Rituximab works against CD20, but not active against Hodgkin Lymphoma.

## 16. MULTIPLE MYELOMA

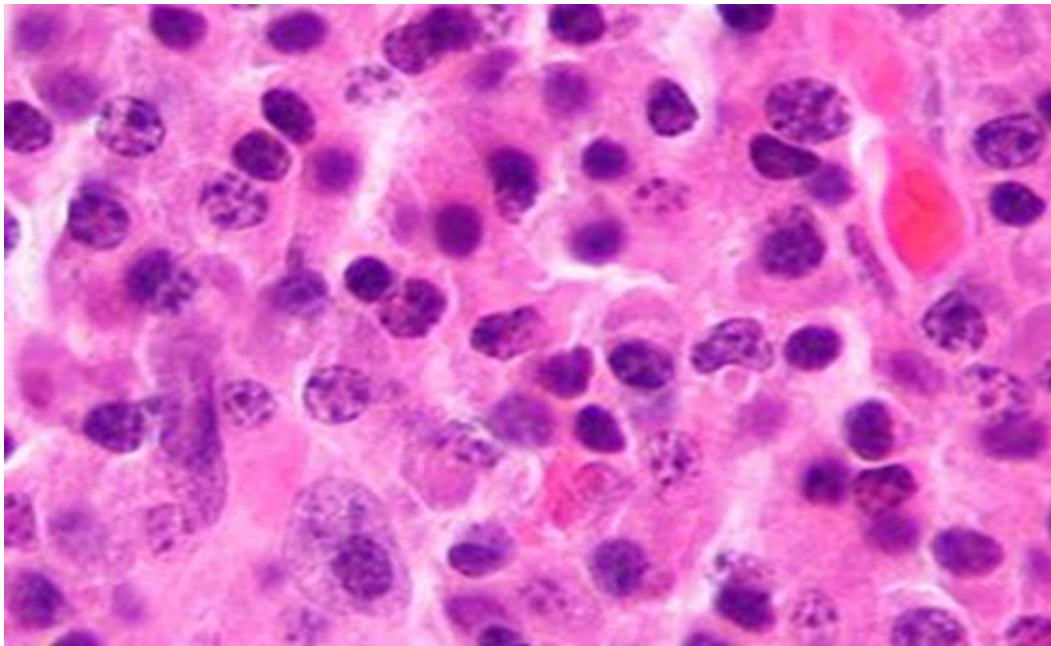


Fig. 14. Multiple myeloma [39]

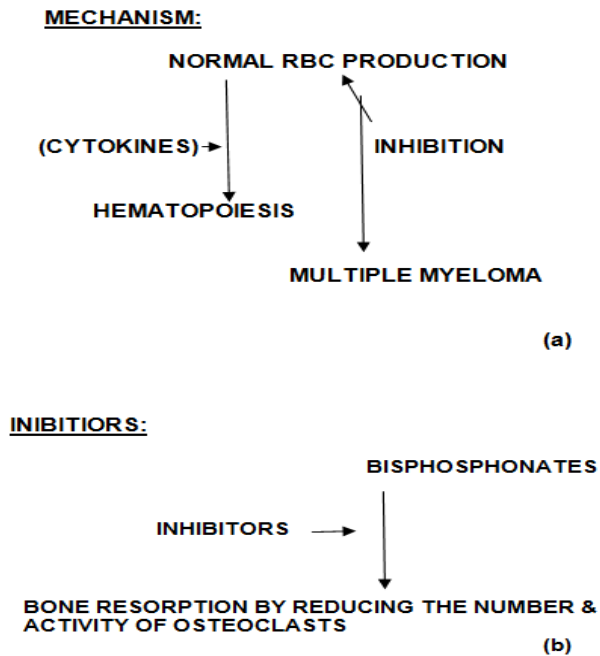


Fig. 15. (a) Development of multiple myeloma (b) mechanism of action of inhibitors used in multiple myeloma

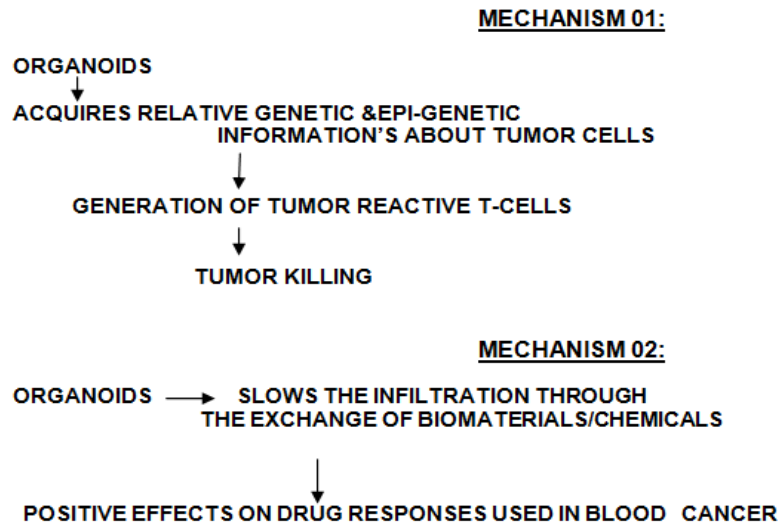
## 17. LIMITATIONS OF THE THEOREM

The vulnerabilities of the current proposal are:

- The Organoids are imperfect for reproductions [6].
- It can affect the therapeutic potential.

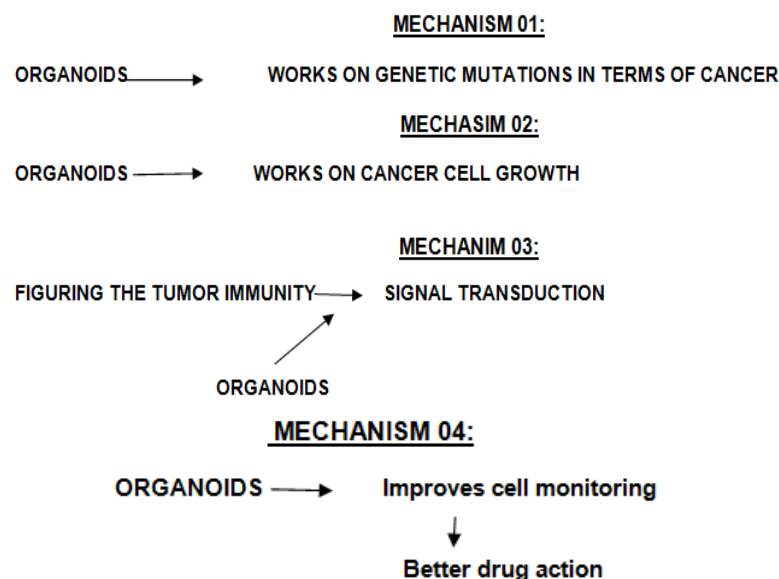
- Some organoid lines cannot be expanded, in case of long Term prospects [6].
- Cancer organoids tends to grow slowly [6].
- It just a research proposal, which requires to be worked gradually on the progression of the
- Developmental procedure.
- In this study there is not any discussion about the acute monocytic leukemia and it's possible
- Treatment.

**18. OUR PROPOSED IN GENERAL ORGANOIDS WORKING DIAGRAM (IN VIVO CONDITION)**



**Fig. 16. Our proposed various mechanism of action (in-vitro condition) (Mechanism 1 & mechanism 2)**

**OUR PROPOSED IN GENERAL ORGANOIDS WORKING DIAGRAM (In vitro CONDITION):**



**Fig. 17. Different types of mechanism of our proposed organoids mechanism of action (In-Vivo Condition) (Mechanism01, 02, 03, 04)**

## 19. ROLE OF ORGANOIDS IN VARIOUS TYPES OF CANCER

**Stomach Cancer:** In stomach cancer, organoids having the capability to play a crucial role in the recapitulation of the Indigenous tumors excluding the architectures, leading to the prevention of mutations by the usage of gastric cancer markers: Carcinoembryonal antigen, Cytokeratin 7 (Krt 7) etc [5].

**Intestinal Cancer:** Colorectal cancer organoids propagates from various sources & shows resemblance with tumors in the aspect of histological analysis. Additionally, the proteomic analysis signifies proteomic managements [5].

**Liver Cancer:** Histologically, in primary liver cancer, organoids possessing the capability to recapitulate from indigenous tumor cells to a certain extent & reflecting transcriptomic alterations to figure out the origins [5].

**Pancreatic Cancer:** The driver gene alterations leads to metabolic changes which is being induced b anticancer drugs. Plays a significant role on organoids in the development of possible action against pancreatic cancer [5].

**Breast Cancer:** Organoid lines were consistent with parent tumor morphology leading to human

epidermal growth factor receptor-2, representing a useful tool in tumor [5].

**OTHER FORMS OF CANCER:** Various organoid models established in the treatment of different cancer treatment works spontaneously infiltration in primary brain organoids & forms hybrid organoid molecules to depict an invasive tumor phenotype & shows an anti-invasion strategies for this type of diseases [5].

## 20. IMMUNOMODULATION INDUCED BY ORGANOID CULTURE

In our studies, the Organoid molecules expressed an extent of immunomodulatory actions in our organoid cultures. Gene expression of T-cell-specific immunomodulator in organoids shows the characteristics to express a normal cancer organoids. Additionally, the transcription of genes with T-cell stimulatory factors like; *TNFSF4* or *TNFSF9* was not altered in cancer organoids compared to normal stem cell organoids. However, expression of human leukocyte antigen (HLA), encoding major histocompatibility represents antigens to T cells, were significantly downregulated in cancer organoids to a well-described phenomenon found in cancers [40].

**Table 4. Abbreviation**

Acronym	Full form
MRI	Magnetic Resonance Imaging
EPI	Epigenetic
3D	Three Dimensional
2D	Two Dimensional
ECM	Extracellular Matrix [41]
DMEM	Dulbecco's Modified eagle's Medium
F-12	Ham's f-12
FBS	Fetal Bovine Serum
HGNC	Hugo Gene Nomenclature Committee
FGF	Fibroblast Growth Factor
SHH	Sonic Hedgehog Ligand
HDAC	Histone Deacetylase
HDI	Histone Deacetylase Inhibitors
HHI	Hedgehog Signaling Inhibitors
FDA	Food and Drug Administration
SMO	Smoothed Protein
CD	Cluster of Differentiation
PET-CT	Positron Emission Tomography-Computed Tomography
MOPP	M=Mustergin, o=Oncovin, p=Procarbazine, p=Prednisone
MDR	Multidrug Resistance Transporter
ALDH	Aldehyde Dehydrogenase
SC	Stem Cell
CSC	Cancer Stem Cell
HLA	Human Leukocyte Antigens

## 21. CONCLUSION

The efficiency of organoid molecules and its prowess towards various types of blood cancer, showing a significant active role to establish an ideal *in vivo-vitro* models. However, the upwardly discussed results and their experiments bespeaking the possible crucial interventions against the cell growths. The role of a 3D cell cultured organoid technology is very useful in terms of possible blockage to the affected tumor stem cells and aiding the transduction mechanism of the normal cell molecules.

Here, The Nano-ranged MRI technology not just only been restricted to its application towards cancerous medications and diagnosis, but also has the power to instrument furtherly to cease the whole associated challenges by providing a possible greater diagnosis and innovative regenerative solutions for the future novel anti-blood cancer therapies.

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## COMPETING INTERESTS

Author has declared that no competing interests exist.

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