ISSN : 2456-7825

SRHU MEDICAL JOURNAL

SRHU Medical Journal

Vol 2 / Issue 2 / Oct-Dec 2024
https://journal.srhu.edu.in/

A publication of
Swami Rama Himalayan University, Dehradun, India

Review Article

SRHU MEDICAL JOURNAL

Consent in Obstetrics and Gynaecology Practice: Ethical, Legal, and Clinical Perspectives

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Consent is universally regarded as the cornerstone of ethical, legal, and professional medical practice. Within the discipline of obstetrics and gynaecology (OBGYN), where interventions frequently involve intimate examinations, reproductive decision-making, and surgical procedures that may permanently alter fertility and bodily integrity, the principles of informed consent assume even greater significance. In such contexts, consent not only fulfils a legal requirement but also ensures the preservation of patient dignity, trust, and autonomy.

This article reviews the conceptual and ethical foundations of consent, explores the Indian legal framework governing consent, discusses its different forms and essential components, and examines documentation standards with a particular emphasis on obstetric and gynaecological care. It further considers special clinical situations such as sterilization, caesarean section, hysterectomy, and abortion, as well as issues pertaining to sexual and reproductive health services. By discussing relevant legal statutes, judicial pronouncements, and international ethical guidelines, the article highlights the challenges faced by clinicians and proposes strategies to enhance patient-centred consent practices in India.

Keywords: Informed consent, Obstetrics and Gynaecology, Reproductive rights, Medico-legal ethics, India

Introduction

Consent in medicine is not merely a procedural formality that precedes treatment or surgery. Rather, it is an affirmation of respect for human dignity, bodily integrity, and patient autonomy. It acknowledges the individual's right to self-determination and establishes the foundation for a trust-based doctor–patient relationship. Within the Indian context, however, the process of obtaining consent is complicated by wide variations in literacy levels, deeply rooted cultural norms, strong family involvement in decision-making, and limited awareness of individual rights (1,2). These contextual realities necessitate a careful balance of ethical principles, clinical realities, and legal mandates in the process of securing informed consent in India.

In obstetrics and gynaecology, the centrality of consent is heightened by the intimate nature of examinations and the long-term implications of many procedures. Decisions about caesarean delivery, hysterectomy, abortion, or sterilization may not only impact the woman's immediate health but also affect her fertility, marital relationships, and future reproductive opportunities. Consequently, the process of consent in this specialty extends beyond routine disclosure of medical risks to include sensitive discussions about sexuality, reproductive choice, and social implications.

Despite its ethical significance, medical education in India has historically prioritized technical proficiency over communication and affective skills. This imbalance has led many practitioners to regard consent primarily as a legal safeguard rather than as an interactive and ongoing dialogue with patients.

Cite this article as: Das S., Chhabra HS, Das P., Consent in Obstetrics and Gynaecology Practice: Ethical, Legal, and Clinical Perspectives. SRHUMJ. 2024;2(2);

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Manuscript received: 01.09.24; Revision accepted: 05.11.24

Obtaining consent is a process and not just an event.

The Concept of Consent: Legal and Ethical Dimensions

The Indian Contract Act of 1872 defines consent as the agreement of two or more persons upon the same thing in the same sense [4]. In medicine, this definition translates into informed consent, whereby the patient voluntarily agrees to a proposed medical intervention after comprehending its nature, benefits, risks, and available alternatives.

From an ethical perspective, consent reflects the principle of autonomy as articulated in Beauchamp and Childress' framework of biomedical ethics [5]. It is intrinsically linked to **beneficence**, which obliges clinicians to act in the patient's best interests, and to **non-maleficence**, which requires avoidance of harm. Consent also has a protective role for physicians, shielding them from allegations of assault, battery, or negligence when appropriately obtained.

Globally, the concept of consent has evolved from a paternalistic model, where physicians were considered the primary decision-makers, to a more nuanced process of shared decision-making. In this modern framework, the clinician not only discloses relevant information but also engages with the patient in deliberation, respects the patient's values and cultural background, and supports decisions that align with her preferences and life circumstances.

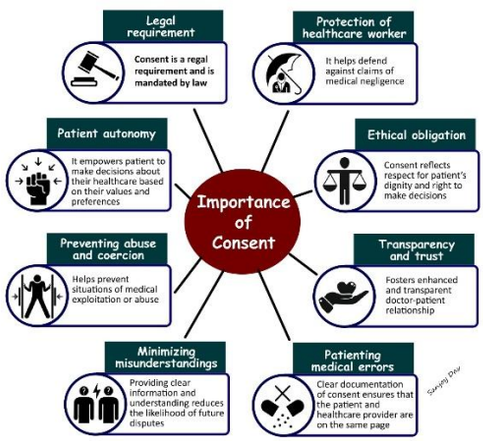

Fig. 1: Importance of consent in medical practice

Types of Consent in Obstetrics and Gynaecology

Consent in medical practice can be classified into implied, expressed, including increasingly documented forms, such as written and video consent.

Implied consent applies in routine, non-invasive procedures, for example, when a patient extends her arm for blood pressure measurement. However, this form of consent has a limited scope and cannot be extended to intimate or invasive examinations.

Expressed consent is necessary for all procedures that involve the genital, pelvic, or breast region, as well as for invasive interventions such as surgeries, abortions, and sterilizations. Expressed consent may be oral, written, or video-recorded. Oral consent is generally considered sufficient for minor, low-risk procedures such as injections and dressings. Written consent is mandatory for high-risk or irreversible procedures such as caesarean section, hysterectomy, or sterilization, and provides tangible documentary evidence of the patient's agreement. In recent years, video consent has been encouraged in high-stakes interventions, particularly in sterilization camps or clinical trials, as it provides clear proof of disclosure, patient understanding, and voluntariness.

Equally important is the concept of **informed refusal**, whereby a patient declines a recommended treatment despite having been informed of its potential benefits and risks. Such refusal must be meticulously documented, as it demonstrates respect for the patient's autonomy and also protects the physician from future legal disputes. For example, if a woman refuses a blood transfusion due to religious beliefs, or declines a caesarean section despite medical advice, her decision must be clearly recorded along with the counselling provided.

Essential Elements of Valid Consent

For consent to be considered legally and ethically valid, it must meet four essential criteria:

- **Disclosure** must be adequate and comprehensible, covering the diagnosis, treatment plan, risks, benefits, alternatives, and consequences of refusal. This information should be conveyed in simple, non-technical language and in the patient's preferred language, taking into account literacy levels and cultural sensitivities.
- The patient must have the **capacity to comprehend** the information and make a rational decision. Special safeguards are required for vulnerable groups such as minors, women experiencing psychological distress during labour, or those with mental illness.

- The element of **voluntariness** is fundamental. Consent must be given freely, without coercion, intimidation, or undue influence. In India, where family members often exert considerable influence over medical decisions, clinicians must prioritise the woman's autonomy above external pressures.
- **Documentation** is critical. Valid consent requires not just the patient's signature but also the recording of names, dates, and times (SNDT). Consent must be procedure-specific; blanket or omnibus consent forms are legally invalid. Ideally, a neutral witness, such as a nurse, should also attest to the process to prevent allegations of coercion.

Documentation Standards

Robust documentation of consent is essential, both for ethical compliance and for medico-legal protection. Consent forms should be bilingual or written in regional languages, avoiding medical jargon and providing simple explanations. Pre-prepared information sheets for common procedures, including details of risks, alternatives, and costs, are valuable tools in enhancing patient understanding.

The process of obtaining consent should include verification of patient comprehension, often achieved through open-ended questions or patient "teach-back." Witness signatures help establish voluntariness, and records must be stored securely to ensure confidentiality. In emergencies, when obtaining written consent may be impossible, treatment may proceed under the doctrine of implied consent, and it will be presumed that the law has given consent. However, the rationale for such action must be documented in detail.

Special Clinical Scenarios

Sterilization, as a permanent contraceptive method, demands particularly stringent standards of disclosure and voluntariness. The Supreme Court in *Devika Biswas v. Union of India* (2016) condemned coercive sterilization practices in mass camps and underscored the principle of informed choice [(6)]. For minors or women with intellectual disability, guardian consent alone may not suffice; court approval may be necessary.

In a **caesarean section**, written consent is obligatory in elective procedures. In emergencies, however, where delay may threaten maternal or fetal life, implied consent under the doctrine of necessity may apply, though detailed documentation is essential. Women must be counselled on the risks of surgery, implications for future pregnancies, and alternatives to surgical delivery.

Hysterectomy carries profound physical, hormonal, and psychological consequences. Reports of unnecessary hysterectomies in India, particularly among young rural women, prompted judicial scrutiny. The Supreme Court directed that hysterectomies in public hospitals be medically justified and audited to prevent misuse [(7)].

Abortion is governed by the Medical Termination of Pregnancy Act (1971, amended in 2021), which expanded access and confidentiality protections [(8)]. The woman's consent alone is sufficient, with guardian consent required only for minors or women with mental illness. Courts have permitted abortions beyond statutory gestational limits in cases involving rape or severe fetal anomalies, as seen in the *X v. Union of India* series of cases [(9)]. Confidentiality of patient identity is strictly mandated under both the MTP Act and the Indian Penal Code.

Consent in Sexual and Reproductive Health Services

In sexual and reproductive health, informed consent is central to the provision of services such as contraception, HIV testing, and abortion. The informed consent of an adult woman is sufficient for contraceptive services, and spousal consent is not legally mandated, although it may be encouraged for mutual understanding and prevention of marital discord. The HIV/AIDS (Prevention and Control) Act of 2017 requires written consent and mandatory counselling before testing, while also safeguarding confidentiality [(10)]. The POCSO Act of 2012 sets the age of consent at 18 years, thereby classifying all sexual activity below this age as statutory rape, irrespective of consent [(11)]. This creates significant dilemmas for clinicians providing reproductive health services to adolescents, as they must balance mandatory reporting requirements with their ethical duty to care. In *A (Mother of X) v. State of Maharashtra* (2024), the Bombay High Court emphasised that even when guardian consent is legally required for abortion, the minor's own views must be given due weight, reaffirming the importance of autonomy [(12)].

Challenges in the Indian Context

The challenge in India lies in ensuring sexual autonomy while balancing legal frameworks designed

for protection. For medical practitioners, knowing where the boundaries lie and documenting consent properly is both a legal shield and a moral obligation.

Table 1: Consent in various procedures and situations

Procedure / Context	Minimum consent form	Who must consent	Extra notes
Routine, non-invasive examination (e.g., BP, auscultation)	Implied	Adult patient (≥18, capacitated)	Limit to routine, non-invasive acts; intimate/invasive exams need express consent.
Intimate examination (breast, pelvic, per-rectal, genital)	Express (oral → preferably written)	Adult patient; for minors/mentally ill: guardian + patient's assent	Take separate, specific consent for each step; document chaperone presence.
HIV testing	Written informed consent (with pre- & post-test counselling)	Adult patient; minor's guardian	Confidentiality is statutorily protected; disclosure is only as permitted by law.
Other STI / HPV testing	Written (best practice)	As above	For adolescents, balance care with POCSO S. 19 mandatory reporting.
MTP ≤ 20 weeks	Written (Form C)	Adult woman herself	Opinion of one RMP is sufficient. Confidentiality protected under S. 5A.
MTP 20–24 weeks (Rule 3B categories)	Written (Form C)	As above	Needs opinion of two RMPs. Categories: minors, rape survivors, disability ≥40%, mental illness, change in marital status, humanitarian/disaster, etc.
MTP >24 weeks (substantial foetal abnormality)	Written (Form C) + Medical Board approval	As above	SC in A (Mother of X) v. State of Maharashtra (2024) calls narrowness of S. 3(2B) "arguably suspect"; courts may still grant relief on constitutional grounds.
Minor seeking / refusing MTP	Written (Form C by guardian) + document the minor's own view	Guardian formally; minor's view is an important factor	POCSO S. 19 report mandatory; per X v. Principal Secretary (2022), identity may be anonymised to protect confidentiality.
Female / male sterilisation	Written	Only the person undergoing sterilisation	Spousal consent is not legally required (encourage discussion, not mandate). Use AV consent in camps as per FP guidance.
LARC(e.g., Copper-T, implants)	Written	Woman herself	Document counselling on side effects, reversibility, and alternatives.
Telemedicine consult (video)	Implied if patient initiates; explicit (text/email/video) if doctor initiates	Patient	Record consent in EMR/chat log; for high-risk SRH advice, follow up with written consent when feasible.
Audio-visual (video) consent (high-stakes procedures, trials, sterilisation camps)	AV recording + Written	Patient/guardian (as applicable)	Capture identity verification, disclosure, Q&A, explicit agreement; encrypt & retain per policy.
Clinical trials (SRH drugs/devices, vulnerable populations)	Written + Audio-Visual (for vulnerable)	Participant / LAR	EC approval mandatory; ongoing re-consent for protocol changes; stringent data privacy.

Recommendations for Practice

To strengthen consent practices in obstetrics and gynaecology, several measures are necessary. Communication and ethics modules must be incorporated into undergraduate and postgraduate curricula to equip clinicians with the skills to obtain meaningful consent. Hospitals should adopt standardized bilingual consent forms, supplemented by patient information leaflets tailored to local languages and literacy levels. The use of video consent should be encouraged in high-risk or irreversible procedures such as sterilization. Regular medico-legal audits and workshops can improve compliance and reduce the risk of litigation. Above all, clinicians must adopt a patient-centred approach, prioritising the woman's autonomy over spousal or familial influence, and advocating for legal reforms that balance mandatory reporting obligations with adolescents' rights to safe reproductive healthcare.

Conclusion

Consent in obstetrics and gynaecology extends beyond the boundaries of legal formality and enters the realm of ethical responsibility and patient empowerment. It is a dynamic process of dialogue, understanding, and respect for women's autonomy. In the Indian context, where sociocultural and systemic barriers complicate decision-making, clinicians bear a heightened responsibility to ensure that consent is informed, voluntary, and comprehensively documented. The medico-legal framework, reinforced by constitutional jurisprudence and judicial oversight, situates consent at the heart of reproductive rights and clinical ethics. By embracing transparent, culturally sensitive, and patient-centred consent practices, healthcare providers can uphold ethical standards, strengthen trust, and safeguard themselves against litigation while promoting women's health and dignity.

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Original Article

SRHU MEDICAL JOURNAL

Novel approach to treat lymphoblastic leukemia "Kymriah" and its scope in India

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Acute lymphoblastic leukemia is a type of cancer which occurs when a bone marrow cell develops errors in its DNA and affects the white blood cells. Kymriah is first FDA approved gene therapy which treats B-cell acute lymphoblastic leukemia (ALL) in patients aged 25 years and younger. It is used in patients whose cancer has relapsed or is refractory. It is formulated in-vivo using a patient's T cells and a gene, code for a special receptor called chimeric antigen receptor (CAR). It is reprogrammed to destroy cancerous B-cell and is administered by IV infusion. Tisagenlecleucel is a CD19-directed genetically modified autologous T cell immunotherapy marketed as Kymriah by Novartis. The whole process takes 22 days as the T cells from a person with cancer are removed, genetically engineered to make a specific T-cell that reacts to cancer, and transferred back to the person. It was invented and initially developed at the University of Pennsylvania; Novartis completed development, obtained FDA approval, and markets the treatment. In August 2017, it became the first FDA-approved treatment that included a gene therapy step in the United States. It is administered in a single treatment, which will have high cost, if not successful money is refunded. Present study highlight first gene therapy based "LIVE" treatment for lymphoblastic leukemia and conducts a survey on knowing the attitude of Indian population towards gene therapy to understand the scope of Kymriah in India.

Keywords: Kymriah, lymphoblastic leukemia, Tisagenlecleucel, Gene therapy

Introduction

Tisagenlecleucel marketed as Kymriah is a treatment for B-cell acute lymphoblastic leukemia which uses the body's own T cells to fight cancer. Kymriah is a genetically modified autologous T-cell immunotherapy. Each of its doses is a tailored treatment created using an individual patient's own T-cells, a type of white blood cell known as a lymphocyte. It is used to treat acute lymphoblastic leukemia which has been relapsed or in the refractory stage.

T cells from a patient suffering from cancer are removed, genetically engineered to make a specific T-cell receptor that reacts to the cancer, and transferred back to the person. The T cells are programmed to target a protein called CD19 that is common on B cells. A chimeric T cell receptor ("CAR-T") is expressed on the surface of the T cell. It was invented and earlier developed at the University of Pennsylvania after that Novartis completed development, obtained FDA approval, and marketed the treatment. In August 2017, it became the first FDA-approved chimeric treatment that included a gene therapy step in the United States. [1]

In this study, we draw special attention to first gene therapy based "LIVE" treatment for lymphoblastic leukemia and conduct a survey on knowing the attitude of Indian population towards gene therapy to understand the scope of Kymriah in India.

Cite this article as: Khadanga A., Yadav N., Chaudhary M., Novel approach to treat lymphoblastic leukemia "Kymriah" and its scope in India. SRHUMJ. 2024;2(2);

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Manuscript received: 12.08.24; Revision accepted: 15.10.24

Methodology

This study was divided in two parts 1. Generation of literature based data 2. Questionaire based survey. Literature based searched was done using online databases Medline, Pub Med from NCBI and Google scholar to know the awareness about first gene therapy based "LIVE" treatment for lymphoblastic leukemia. The keywords Kymriah, lymphoblastic leukemia, Tisagenlecleucel etc. were used for searching. Furthermore, a questionnaire based survey was conducted on knowing the attitude of Indian population towards gene therapy to understand the scope of Kymriah in India. So, a customised questionnaire was prepared and survey was conducted on healthy volunteers (n= 250) in including male and female in 20 to 50 years about knowing the attitude of Indian population about gene therapy "KYMRIAH".

History of Therapy Development

This treatment was developed by a group headed by Carl H. June at the University of Pennsylvania and is licensed to Novartis. In August 2017, Kymriah (CTL019) received get through therapy designation by the US FDA for the treatment of relapsed or refractory diffuse large B-cell lymphoma.This treatment will be administered at specific medical centers where staff has been highly trained to manage possible side effects to this new type of treatment.[2]

Acute lymphoblastic leukemia

Adult acute lymphoblastic leukemia (ALL) is a form of cancer in which the bone marrow makes too many lymphocytes. Leukemia may affect red blood cells, white blood cells, and platelets.

Occurs fewer than 1 million cases per year (India).Acute lymphoblastic leukemia is the most common childhood cancer. It occurs when a bone marrow cell develops errors in its DNA making abnormal amount of WBC. Symptoms are enlarged lymph nodes, fever, bone pain, bruising, bleeding from the gums and frequent infections.[3]

Acute Lymphoblastic Leukemia can be of B- cell or T-cell origin. B-cell precursor. ALL in paediatric and young adult patients is characterised by a common antigen on the membrane of the cell in the majority of cases, not only at initial diagnosis, but also at relapse. This antigen is called CD19. About 80-85% of paediatric ALL diagnosis are B-cell precursor in origin and CD19 positive.

CD19 Expression is restricted to B lineage cells and is not expressed by any pluripotent blood stem cells. Since CD19 is present only to B cell, the effect of an anti-CD19 agent would chiefly affect B-cell function. CD19 is expressed by B-cell malignancies in particular B-cell precursor ALL. This made CD19 a natural target for immunotherapy. [4]

The strategy with tisagenlecleucei was to produce genetically engineered chimeric antigen receptor (CAR) T cells transfixed with chimeric receptor genes to combine the effectors functions of T lymphocytes with the ability of antibodies to recognize predefined surface antigens with high specificity in a non-MHC restricted manner. The target was CD19 on the surface of the B-cell precursor blasts. Paediatric and Young Adult B-cell Precursor Acute Lymphoblastic Leukemia Acute lymphoblastic leukemia (ALL) occurs in children and adults.[1]

Mechanism of Action

KYMRIAH is a customised therapy that reprograms a patient's own T cells with a chimeric antigen receptor (CAR) containing a 4-1BB co stimulatory domain. The 4-1BB co stimulatory domain is responsible for enhancing the expansion and persistence of KYMRIAH.

The KYMRIAH CAR also contains a CD3? intracellular signalling domain, which is important for initiating T-cell activation and antitumor activity. [6]

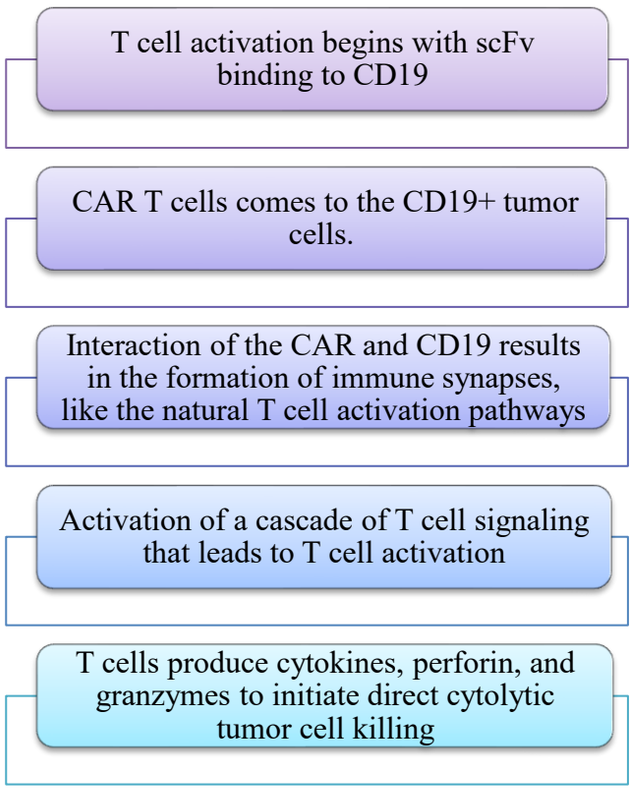

Figure 1 : Mechanism of action is the direct cytolytic killing of tumour cells.

Product Description

KYMRIAH is composed of autologous T cells that are genetically modified with a lenti-viral vector which encodes a chimeric antigen receptor (CAR). The CAR specifically recognizes the CD19 protein present on CD19+ B lineage tumour cells as well as normal B cells.

Dosage and Half Life

KYMRIAH is given in a single-dose unit containing chimeric antigen receptor (CAR)-positive viable T cells based on the patient weight which is reported at the time of leukapheresis. For patients 50 kg or less: administer 0.2 to 5.0 x 106 CAR-positive viable T cells per kg body weight. For patients above 50 kg: administer 0.1 to 2.5 x 108 CAR-positive viable T cells. The mean half-life was 16.8 days in paediatric and young adult relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) patients. [7]

Clinical Pharmacology

KYMRIAH displayed an initial quick expansion phase achieving maximal concentration (Cmax) around day 10 followed by a slower bi-exponential decline in complete remission/complete remission with incomplete hematologic recovery (CR/CRi) patients on day 28.

Cmax and AUC0-28d of KYMRIAH were higher in CR/CRi patients as compared with non-response patients.

No difference in the pharmacokinetics of KYMRIAH was noted for gender and different race. Children, less than 10 years of age have higher Cmax and AUC about 1.5 to 2-fold higher than adults. Both Cmax and AUC0-28d decreased with increasing age. However, due to small sample size and high variability, it was difficult to evaluate a definitive impact of age on the PK of KYMRIAH. [7]

Efficacy

Approval of the treatment was based on a single-arm trial of 63 paediatric patients with precursor B-cell ALL.3 Patients received a single dose of tisagenlecleucel intravenously within 2 to 14 days following completion of lymphodepleting chemotherapy of fludarabine and cyclophosphamide.

The confirmed overall remission rate at 3 months was 82.5% (95% confidence interval [CI], 70.9-91.0), which is significantly higher than the alternatives.

Storage Condition: Kymriah comes from the manufacturer as a frozen suspension. It should be stored in the vapour phase of liquid nitrogen at less than or equal to -120 °C.[8]

Lab to Patient: Product Delivery

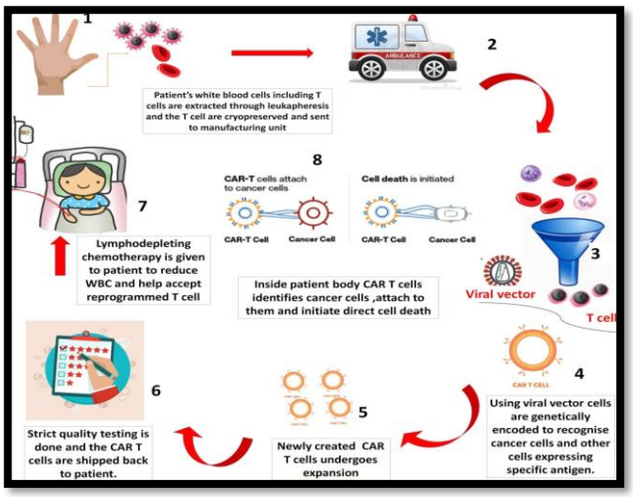

Figure 2: Shows that all steps involves in preparation from lab processing to patient delivery

Steps involved in Processing of Product

- **Blood Filtering**

At the hospital, the patient's immune T cell is taken from the blood, frozen and transported to the Novartis plant.

- **Reprogramming**

It genetically programs the T cells to recognise a distinctive marker on B cells which turn malignant for leukemia.

- **Expansion**

The modified T cells are multiplied for over 3- 4 weeks, frozen and shipped back to the hospital for the patient.

- **Preparing The Patient**

The patient gets some chemotherapy to kill some white blood cells and help the body to accept the modified T cell.

- **Infusion**

The modified T cells are infused back into the patient's vein.

- **Attacking The Cancer**

The T cells attack on the malignant B cells and kill cancer. [6]

Inclusion criteria for Kymriah: Patients are applicable for KYMRIAH if

They have not gone into remission following frontline treatment (primary refractory)

Have relapsed and cannot achieve remission (chemo refractory)

Have had second or subsequent relapse after complete remission or stem cell transplant (SCT)

Monitoring:

- **Short-term monitoring**

Patients should stay within 2 hours of their KYMRIAH Treatment Center for at least 4 weeks after infusion to monitor for, and treat, potential side effects. Caregivers should also remain with the patient to check for signs of fever or other side effects.

- **Long-term monitoring**

Routine long-term monitoring is required for potential secondary malignancies. Patients should be informed about, and encouraged to participate in, the KYMRIAH registry. [9]

Cost for Magic Life Saving Therapy

It is Single dosage administered treatment, which will cost $475,000. Novartis says that this treatment is cheaper than some bone marrow transplants. Novartis will not charge patients who have not responded to the treatment. [10]

Side Effects

Cytokine release syndrome (CRS), which is a systemic response to the activation and proliferation of CAR T-cells causing very high fever and flu-like signs, and for neurological events

Low blood pressure (hypotension)

Acute kidney injury

Fever and decreased oxygen (hypoxia) [6]

Survey Results: Results are summarized in Figure 3 and 4.

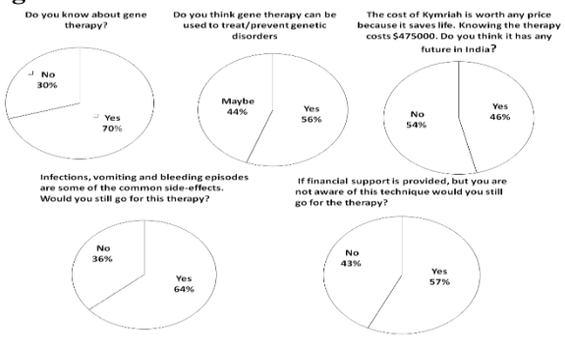

Figure 3: Shows survey responses in population with age 20-50 Years in 250 subjects including male and female resident of NCR.

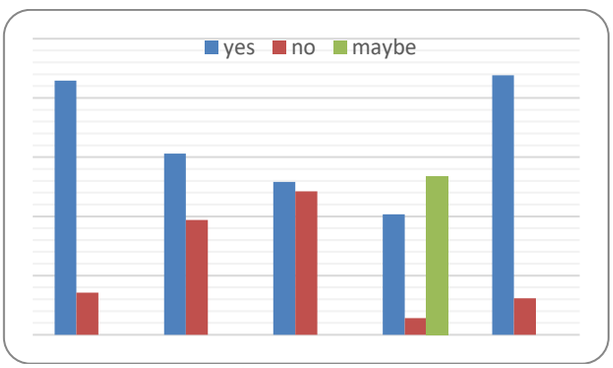

Figure 4: Shows survey responses

Conclusion

This ground breaking customize treatment of curing cancer has a lot of potential in treating the patient suffering from leukemia. This treatment has shown a massive response rate in people with these cancers. It's given hope to patients and parents. If other treatments fail, they can go for this drug that teaches our cells to fight cancer. This treatment should also be approved in India as its cost is comparably less and effective than other treatments. From the survey conducted most respondents about 70% indicated prior knowledge about gene therapy; the proportion responded considering gene therapy is high as 88% which is quite good and for genetic enhancement. Concern for side effects is very less. And acceptability of Kymriah as per Indian scenario is also good. So, we can say that if this treatment is brought to India it will have a success rate higher than expected.

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Review Article

SRHU MEDICAL JOURNAL

Microglia in Epilepsy: From Circuit Modulators to Therapeutic Targets

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Epilepsy affects over 50 million people worldwide, with one-third resistant to drugs. Once seen as a disorder of neuronal hyperexcitability, it's now recognized as involving complex network dysfunction, where non-neuronal cells, especially microglia, play active roles. Microglia regulate synaptic activity, immune surveillance, and circuit remodeling. They monitor extracellular changes, detect ATP from hyperactive neurons, and respond with process motility. Studies show microglia can both reduce hyperactivity by spine contact and promote excitation by stimulating dendritic filopodia and new synapses. This dual role places microglia at the junction of stability and hyperexcitability. Evidence links maladaptive microglial responses to epileptogenesis, seizures, and network instability, highlighting the importance of glial and immune pathways as therapeutic targets.

Keywords: Microglia–neuron interactions; Epileptogenesis; Neuroinflammation; Glial therapeutic targets

Introduction

Beyond Neurons: Microglia at the Crossroads of Epilepsy and Brain Health

Across the globe, epilepsy poses a significant health challenge, affecting around 1% of the population with serious medical, social, and economic consequences (Fiest et al., 2017; Feigin et al., 2019). Despite the availability of various anti-seizure medications, about 30% of patients don't respond to treatment, highlighting the limitations of current therapies that mainly target neuronal ion channels and neurotransmitter systems. The ongoing burden of drug-resistant epilepsy calls for the scientific community to rethink the cellular and molecular foundations of epileptogenesis and seizure dynamics (Fonseca-Barriendos et al., 2021).

Historically, epilepsy research has focused on neurons, emphasizing abnormal synaptic transmission, channelopathies, and imbalances between excitatory and inhibitory signals. While neurons are clearly key to epileptic discharges, this perspective overlooks the contributions of glial cells and the neuroimmune system.

In recent decades, a paradigm shift has taken place: microglia, astrocytes, and oligodendrocytes are increasingly recognized as active participants in shaping neural circuit excitability (Shen et al., 2022). Microglia, in particular, have emerged as versatile regulators that sense, integrate, and respond to neuronal and environmental signals, positioning them as both protectors and potential instigators of pathological network activity (Wu et al., 2020).

Microglia are unique among CNS cells in their origin, biology, and functions. Derived from yolk sac progenitors that immigrate to and colonize the early developing brain before the blood–brain barrier closes, microglia maintain a self-renewing, long-lived population distinct from peripheral monocytes (Hattori, 2023).

Cite this article as: Kala R., Srivastava G., Bisht K. Sharma KP, Microglia in Epilepsy: From Circuit Modulators to Therapeutic Targets, SRHUMJ. 2024;2(2);

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Manuscript received: 25.08.24; Revision accepted: 01.11.24

Once viewed as passive "resting" cells in health, they are now recognized as dynamic surveyors of the parenchyma, constantly extending and retracting processes to monitor their environment. This surveillance is made possible through a rich repertoire of receptors collectively termed the sensome, enabling microglia to detect ATP, chemokines, neurotransmitters, and danger-associated molecular patterns (Hickman and El Khoury, 2019).
Within this sensome, the purinergic receptor P2RY12 plays a central role, mediating rapid responses to ATP/ADP gradients released during neuronal activity or injury. High-resolution in vivo two-photon microscopy studies have revealed striking phenomena: microglial processes rapidly extend toward sites of neuronal hyperactivity, forming contacts that can either stabilize spines or lead to their removal (Eyo et al., 2014). Conversely, microglia have been shown to induce the formation of dendritic filopodia and new excitatory synapses, directly modulating circuit function(Miyamoto et al., 2016). Such bidirectional influences underscore the intimate relationship between microglia and neurons, and suggest that in conditions like epilepsy, where neuronal activity is profoundly altered, microglia may tip the balance toward protection or pathology.

This review aims to (i) provide a detailed overview of microglial biology and their sensome, (ii) highlight experimental evidence of microglial regulation of neuronal activity, (iii) integrate emerging data on microglia's role in epilepsy, and (iv) discuss the potential of targeting non-neuronal elements like microglia, astrocytes, and oligodendrocytes as novel therapeutic avenues for epilepsy

Microglial Biology and the Sensome

Microglia are a unique population of brain-resident immune cells, distinct in both origin and function. Derived from primitive yolk sac–derived myeloid progenitors that colonize the early developing brain before the closure of the blood–brain barrier, these immigrant cells establish a self-renewing, long-lived niche within the central nervous system (CNS) (Alliot et al., 1999). This allows them to establish a long-lasting, self-renewing population within the central nervous system. Unlike peripheral macrophages, microglia maintain independence from circulating monocytes, allowing them to evolve specialized functions tailored to the neural environment. During development, they contribute indispensably to neurogenesis, synaptogenesis, angiogenesis, blood–brain barrier maturation, and myelination, highlighting their central role in shaping the structural and functional foundations of the brain (Pont-Lezica et al., 2011).

In the adult brain, microglia have a ramified shape with fine, moving processes that constantly scan the brain environment. This surveillance activity is driven by their diverse sensory machinery, which includes receptors for various chemicals like ATP, ADP, and neurotransmitters (Hickman and El Khoury, 2019). Among these, the purinergic receptor P2RY12 is especially important. In the adult healthy brain, P2RY12 is only found in microglia and distinguishes them from other brain cells (Walker et al., 2020). It helps microglia respond quickly to chemicals released during brain activity, injury, or seizures. Through P2RY12 signaling, microglia extend processes toward overactive or injured neurons, forming dynamic connections that influence how neurons communicate and the excitability of brain circuits.

Downregulation of P2RY12 marks a key transition from a healthy to an activated state, making it a reliable marker of microglial activation (Walker et al., 2020). This dual role serves both as a cell-specific marker and a functional regulator of microglial activity, putting P2RY12 at the forefront of microglial research. In epilepsy, studies have highlighted its critical role in shaping communication between neurons and microglia, modulating brain hyperactivity, and possibly determining whether microglial responses become helpful or harmful (Gibbs-Shelton et al., 2023). Therefore, P2RY12 exemplifies the broader principle that microglial identity and function are closely linked, positioning these cells as essential guardians of brain development, health, and disease.

Microglia-Neuron Interactions: Bidirectional Regulation

Recent advances in in vivo imaging have transformed our understanding of microglia–neuron interactions, revealing a striking bidirectional role for microglia as both regulators of neuronal hyperactivity and facilitators of excitatory connectivity. A seminal study by Davalos and colleagues (2005) provided the first direct evidence that microglial processes are highly dynamic responders to neuronal stress signals (Davalos et al., 2005). Using laser-induced focal injury in cortical slices and in vivo two-photon microscopy, they showed that the local release of extracellular ATP acts as a potent chemotactic signal, rapidly guiding microglial processes toward the site of damage. This discovery not only established ATP

as a “find-me” cue but also set the stage for later studies investigating microglial surveillance of neuronal activity.

Building on this work, two-photon imaging studies demonstrated that microglia preferentially contact hyperactive neurons and dendritic spines in vivo, where they can either stabilize or selectively eliminate synaptic structures depending on the excitatory load (Eyo et al., 2014; Akiyoshi et al., 2018). These contacts are not merely structural: electrophysiological recordings from mice revealed that microglial engagement reduces excitatory postsynaptic currents and dampens neuronal firing, providing direct evidence that microglia exert inhibitory control over hyperactive circuits. Mechanistically, this pruning process has been traced to the complement pathway, where synapses tagged by complement proteins C1q and C3 are engulfed through microglial complement receptor CR3, a mechanism first clarified in landmark studies from Beth Stevens’s group at Boston Children’s Hospital (Stephan et al., 2012).

Paradoxically, microglia can also promote neuronal activity and circuit remodeling. Miyamoto and colleagues working in Riken’s Brain Science Institute under the guidance of Hiroki Nishiyama, used in vivo imaging of mouse somatosensory cortex to demonstrate that microglial contacts with dendritic shafts induce the rapid formation of filopodia, many of which subsequently develop into stable excitatory synapses (Miyamoto et al., 2016). This effect was shown to depend on microglia-derived brain-derived neurotrophic factor (BDNF) acting on neuronal TrkB receptors, thereby directly enhancing excitatory drive. Together, these findings highlight that microglia are not merely passive guardians against hyperexcitability but also active architects of synaptic connectivity, capable of both dampening pathological activity and fostering the structural plasticity that underpins learning and memory.

Together, these dual functions highlight the exquisite sensitivity of microglia to local neuronal states and their capacity to fine-tune network activity. While essential for normal development and homeostatic plasticity, this plasticity may become maladaptive in pathological contexts such as epilepsy, where persistent neuronal hyperactivity could hijack microglial mechanisms of pruning and connectivity, thereby contributing to disease progression.

Microglia in Epilepsy

Increasingly, epilepsy is being seen not just as a disorder of excessive neuronal activity, but also as a long-term inflammation of the brain. Microglia, the brain’s own immune cells, play a key role in this process. Studies using imaging techniques, measurements of fluid surrounding the brain, and examination of brain tissue after surgery have consistently found that microglia are active in people with epilepsy (Kagitani-Shimono et al., 2023). However, the effects of microglia can be both helpful and harmful, depending on the context.

Microglia switch between states of balance and reactivity in response to various factors. During seizures, microglia respond quickly, extending their reach, sensing ATP through P2Y12 receptors (Eyo et al., 2014). These early responses may help reduce nerve damage by clearing excess glutamate and debris, or calming hyperactive neurons using mechanisms discussed earlier. In contrast, microglia stay activated for a long time in people with epilepsy, driven by ongoing seizures, damage to the blood–brain barrier, and a back-and-forth signaling between neurons and microglia (Zhao et al., 2018). Analysis of brain tissue from individuals with epilepsy and experimental models reveals increased activity in genes related to inflammation and cytokines like IL-1β, TNF-α, and IL-6, with single-cell studies highlighting diverse microglial clusters that either promote inflammation or support repair (Mukhtar, 2020). Cytokines like IL-1β are key players in neuroinflammation, which boost neuronal activity through NMDA receptors, reducing GABAergic inhibition, thanks to p38 MAPK pathways (Khan et al., 2023). Medications such as anakinra, which block IL-1β signaling, show promise in reducing seizure severity (Yamanaka et al., 2021). Meanwhile, TNF-α has mixed effects: soluble forms can trigger excitotoxicity, while membrane-bound variants may aid in remyelination (Michev et al., 2021). IL-6 is associated with neuroinflammation and seizure-related damage, exhibiting both growth-promoting and inflammatory roles (Soltani Khaboushan et al., 2022). Additionally, while the complement system helps clear debris, excessive activation can mistakenly eliminate synapses, particularly inhibitory ones, contributing to hyperexcitability. Notably, elevated complement activation is found in the brain tissue of epilepsy patients.

Microglia engage in dynamic, bidirectional communication with neurons. During neuronal hyperactivity, ATP release activates P2X7 receptors on microglia, leading to IL-1β secretion and enhanced excitability (Engel et al., 2012). Chemokine pathways such as CX3CL1–CX3CR1 and purinergic receptors

like P2RY12 usually help restrain microglial reactivity and guide microglial processes toward hyperactive synapses, contributing to network stabilization. Disruption of these signaling mechanisms worsens seizure susceptibility (Gibbs-Shelton et al., 2023).

Contrary to the earlier view of microglia as primarily detrimental in epilepsy, recent evidence shows they also play beneficial roles. Genetic or pharmacological ablation of microglia, or loss of homeostatic receptors such as CX3CR1 and P2RY12, leads to more severe seizures and delayed recovery. In experimental models, microglia help terminate seizures, limit neuronal injury, and promote functional recovery after hyperexcitability (Gibbs-Shelton et al., 2023). Therapeutically, microglial pathways are attractive targets. Blocking P2X7 reduces seizures in animal models, and IL-1R blockade with anakinra shows benefit in paediatric epilepsies (Engel, 2023). Inhibiting CSF1R has also reduced seizures experimentally, while complement inhibition prevents excessive synapse loss. These strategies highlight microglia as both contributors to pathology and key players in endogenous seizure-limiting mechanisms.

In summary, microglia are not simply drivers of neuroinflammation but act as context-dependent modulators of epilepsy. They prune synapses, release cytokines, and remodel networks, yet also restrain seizures and aid recovery. Their duality presents challenges but also rich opportunities for therapeutic targeting.

Translational and Therapeutic Perspectives on Glial Targets in Epilepsy

1. Non-Neuronal Rationale and Microglial Pathways

Current antiepileptic drugs (AEDs) act largely on neuronal ion channels and neurotransmitter systems, yet nearly one-third of patients remain drug-resistant. This therapeutic ceiling has shifted attention toward non-neuronal targets, with glial cells now recognized as active regulators of excitability and network remodeling. Microglia are particularly central, given their ability to sense neuronal activity, release cytokines, prune synapses, and coordinate with astrocytes and oligodendrocytes.

Among microglial pathways, the P2X7 receptor has been extensively studied: ATP released during hyperactivity activates inflammasome signaling and IL-1β release, driving seizures. P2X7 antagonists such as Brilliant Blue G and JNJ-47965567 reduce seizure burden in rodent models, and P2X7 inhibitors already in trials for psychiatric and inflammatory disorders may be repurposed. Conversely, P2Y12 receptors normally guide microglial processes toward active synapses and stabilize networks; their loss increases seizure severity (Gibbs-Shelton et al., 2023). Other inflammatory targets include IL-1R/TLR signaling, with caspase-1 inhibition (VX-765) and IL-1R antagonism (anakinra) showing preclinical and early clinical benefit, particularly in pediatric epilepsies such as FIRES. The complement cascade represents another axis: aberrant C1q/C3-mediated synaptic pruning weakens inhibitory circuits, while complement inhibition preserves interneuron connectivity and reduces seizures. Finally, CSF1R modulation alters microglial survival; inhibitors like PLX3397 attenuate seizures, but full depletion is detrimental, highlighting the need for temporally restricted or partial modulation. Collectively, these findings illustrate that microglia can be both pathogenic drivers and protective regulators, requiring therapies that suppress harmful signaling while preserving seizure-terminating and reparative roles.

2. Astrocytic and Oligodendrocytic Contributions

Previously thought of as passive support cells, astrocytes and oligodendrocytes are now seen as crucial to epileptic network dynamics. Astrocytes control glutamate clearance, potassium buffering, and gliotransmission; problems with glutamate transporters like EAAT2 increase excitotoxicity, while boosting them with ceftriaxone reduces seizures in models (Zaitsev et al., 2019). Excessive connections between cells through connexin-43 enhance synchronization and seizure spread, whereas blocking connexin limits propagation (Wang et al., 2025). Cytokines from astrocytes (IL-6, TNF-α) also increase gliosis and excitability. Notably, communication with microglia worsens the pathology: microglial TNF-α triggers astrocytic glutamate release, creating a self-reinforcing excitatory loop.

Oligodendrocytes contribute through myelination and metabolic support, processes disrupted in chronic epilepsy. Myelin deficits impair conduction and network stability, while inflammatory cytokines hinder myelin repair. Microglia influence the growth of oligodendrocyte precursors, suggesting that interventions promoting myelin repair could reduce seizure susceptibility and prevent cognitive decline. Together, targets in astrocytes and oligodendrocytes complement microglial interventions by addressing the balance between excitatory and inhibitory signals, synchronization, and long-term circuit integrity.

3. Innovative Personalized Strategies and Challenges

Advances in therapeutic platforms are broadening the scope of interventions that target glial cells. Gene and RNA-based therapies, such as using viruses or nanoparticles to deliver anti-inflammatory cytokines (like IL-10 and TGF-β) or targeting pro-inflammatory mediators with antisense oligonucleotides, allow for precise control of glial activity. Nanomedicine also makes it possible to deliver modulators for CSF1R, P2X7, or IL-1R through the blood–brain barrier with fewer side effects. Non-drug approaches, such as vagus nerve stimulation and transcranial magnetic stimulation, may also reduce seizures by modulating the immune system, although the exact mechanisms involving microglia need more research. Meanwhile, cell-based methods, including transplanting astrocytes and replacing microglial cells, have shown promise in preclinical models by restoring balance and improving the body's ability to cope with stress. To successfully translate these findings into clinical use, we'll need precision medicine approaches. Identifying biomarkers, such as specific gene activity, cytokine levels, and PET scans that show activity in P2X7 or TSPO, may help us pinpoint patients who are most likely to benefit. Timing is also crucial: microglia can help control acute seizures but can worsen pathology in chronic cases, so it's essential to target the right stage of the disease. Ultimately, combining glial-targeted strategies with traditional anti-seizure medications may help overcome drug resistance while minimizing side effects.

Despite promise, glial-targeted therapies face challenges. Microglia are highly plastic, exerting protective and pathological effects depending on context, and are involved in indiscriminate suppression. Rodent–human differences in glial biology complicate translation, while epilepsy's heterogeneity means glial contributions vary across syndromes. Long-term suppression of immune signaling raises concerns about infection, cognition, and plasticity. Careful validation, stratified trials, and long-term monitoring will therefore be critical for safe and effective clinical application.

Discussion

Over the past two decades, microglia have come to be recognized not as static immune sentries but as dynamic regulators of neural circuit function. In the healthy brain, they continuously extend and retract processes in response to environmental cues, integrating signals to facilitate both structural and functional remodeling. In vivo imaging studies have shown that microglia calm hyperactive synapses, prune redundant connections, and support the formation of new excitatory inputs through the release of brain-derived neurotrophic factor.

However, this versatility makes microglia vulnerable in epilepsy. Initially protective, their response becomes harmful under recurrent seizures and blood-brain barrier dysfunction, leading to a reactive state. Reactive microglia secrete pro-inflammatory factors and strip inhibitory synapses, lowering seizure thresholds and perpetuating a cycle of inflammation and hyperexcitability. They operate within a glial consortium, where the dysfunction of astrocytes and oligodendrocytes further destabilizes neural circuits, redefining epilepsy as a disorder of glial-neuronal ecosystems. These insights have significant therapeutic value. Targeting microglial signaling pathways and astrocytic or oligodendrocytic functions offers potential for effective interventions. Advanced platforms, such as nanoparticle delivery and cell therapy, promise innovative ways to modulate glial states, but caution is needed as suppressing microglia could impair their beneficial roles.

Future progress hinges on understanding temporal dynamics in glial functions, recognizing species differences, and identifying biomarkers for monitoring glial states. Importantly, we must appreciate patient heterogeneity, as different epilepsy types may involve distinct glial mechanisms. Ultimately, epilepsy should be viewed not merely as an electrical disorder of neurons but as a disruption of neuroimmune ecosystems. By positioning microglia at the core of these networks, we can move towards true disease modification, enhancing resilience, preserving cognition, and restoring brain health.

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Original Article

SRHU MEDICAL JOURNAL

Cultivating Compassion in Medical Students Through Films: A Student Feedback Study

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Background: The National Medical Commission places Attitude, Ethics and Communication (AETCOM) at the core of MBBS training. Yet under crowded timetables, empathy and communication can remain abstract. We explored whether a compact, film-based classroom session ("cinemeducation") could translate these aims into concrete, patient-centred behaviours.

Aim: To measure and promote empathy among MBBS students by integrating a one-hour cinemeducation intervention within an AETCOM slot.

Methods: Cross-sectional, interventional classroom study during a scheduled AETCOM session at Himalayan Institute of Medical Sciences, SRHU, Dehradun (India). Second-year MBBS students (n=145) viewed three short scenes from *The Doctor* (1991). Each scene was paired with a focused prompt and a brisk, guided debrief oriented to "one thing you can do tomorrow." Anonymous end-of-class reflections were summarised via light-touch word-frequency signals; a 4-item feedback form captured acceptability and perceived learning.

Results: Scene-wise discourse showed a clear progression from constraints (e.g., time pressure, burnout) to technique (e.g., warn → name → pause & check; allow silence; invite questions; ensure informed consent) and then to commitments (e.g., warm greeting, using names, eye-level seating, brief emotional check-ins, closing instruction loops). Post-session feedback indicated high acceptability and perceived value: enjoyable/very enjoyable 94%; prefer films for empathy/communication learning 89%; strongly recommend continuing such sessions 92%; reported enhanced understanding of empathy 88%.

Conclusion: A single AETCOM hour built on a scene → prompt → debrief spine is feasible, low-cost, and well-received, and it appears to nudge learners from problem-spotting toward actionable, ethically grounded communication. This approach aligns with NMC's AETCOM intent and merits wider implementation and rigorous follow-up (e.g., delayed reflections, observer-rated behaviours, multi-site studies).

Keywords: AETCOM; cinemeducation; empathy; communication skills; medical humanities; MBBS; India.

Introduction

In India's competency-based MBBS curriculum, empathy, communication, and professionalism are named outcomes. The National Medical Commission (NMC) embeds Attitude, Ethics and Communication (AETCOM) longitudinally from the foundation course through clinical postings.[1–3,10] The AETCOM module explicitly frames communication as foundational to safe, ethical care and provides competencies, session outlines, and assessment guidance. This signals that NMC recognises that these domains deserve protected time and deliberate pedagogy.1–3,9,10

However, in our experience, these values risk becoming abstract under crowded timetables. We therefore trialled a compact, one-hour AETCOM session that used selected scenes from *The Doctor* (1991) to provoke feeling, perspective-taking, and ethically grounded "micro-actions" students can attempt immediately.

Cite this article as: Gangwar K, Chhabra HS, Das S, Tripathi P, Cultivating Compassion in Medical Students Through Films: A Student Feedback Study, SRHUMJ. 2024;2(2)

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Manuscript received: 10.07.24; Revision accepted: 15.09.24

Aims and Objectives

Aim: To measure and promote empathy among MBBS students by integrating a compact, class-embedded cinemeducation intervention within the AETCOM timetable.

This approach known as cinemeducation, has long been described in medical education to enliven ethics, professionalism, and communication.[4,5,7,8] Empathic engagement is associated with better patient outcomes and adherence.[6] So, we felt it reasonable to test classroom designs that help students translate empathy into concrete behaviours early in training.

Objectives:

1. Implement a structured film-based session using three short scenes from *The Doctor* (1991), each paired with a focused prompt and guided debrief.
2. Characterise empathy-relevant attitudes and language expressed by students immediately after the session through scene-wise short-answer reflections
3. Assess acceptability and perceived utility of the session via post-class feedback.
4. Summarise scene-wise reflections of students using light-touch word-frequency signals.

Methodology

Design and setting. It was a Cross-sectional, interventional classroom study during a scheduled AETCOM session at Himalayan Institute of Medical Sciences, SRHU, Jolly Grant, Dehradun, Uttarakhand, India.

Participants. The participants were the MBBS Prof II students (n = 159) who provided consent and completed an anonymous Google Form at the end of the class. Only the consenting students (n = 145) were included and any unwilling or incomplete submissions were excluded (n = 14).

Intervention. Three short scenes from *The Doctor* (1991; lawful copy) were chosen for escalating ethical complexity. After each scene, we posed one focused prompt and conducted a brisk, guided debrief oriented to "one thing you can do tomorrow." This aligns with NMC's AETCOM guidance that positions communication and ethics as teachable competencies with explicit, observable behaviours.[1–3,9]

Prompts.

- Scene 1: Should emotional care be part of daily duties? What gets in the way?
- Scene 2: What could the diagnosing doctor have done differently to make the news manageable?
- Scene 3: Was the role-reversal method effective? How would you apply it?

Data and analysis.

- Scene-wise short answers were pooled for simple word-frequency reads to identify patterns.
- Four Likert-style items captured enjoyment, preference for film-based learning, recommendation to continue, and perceived enhancement of empathy. Descriptive statistics are reported.

Ethics. The activity was part of scheduled AETCOM teaching. Reflection/feedback participation was voluntary, carried no academic credit/penalty, and could be skipped. Data were anonymous. Results have been presented as counts/percentages and summary word-frequency signals. No raw responses have been reproduced. Any illustrative phrasing is paraphrased so that individual students are not identifiable. This feedback was gathered for classroom quality-improvement with anonymous minimal-risk data.

Copyright and access control. Scenes were exhibited solely for classroom/LMS spaces restricted to enrolled learners and faculty under Section 52(1)(j) of the Indian Copyright Act. A lawful copy was used; recording/redistribution was prohibited; a compliance notice and slide footers were displayed. (Operationalisation details available on request.)

Results

Scene-wise reflections (word-frequency signal).

- **Scene 1 — Naming obstacles.** Top terms: "patient" (98), "emotional" (76), "time" (73), "doctor" (63), "doctors" (60), "lack" (32), "burnout" (13). Analysis: students affirmed emotional care yet foregrounded structural constraints (time pressure, workload, limited training, language/culture gaps, institutional supports).
- **Scene 2 — From critique to craft.** Top terms: "patient" (100), "procedure" (84), "news" (82), "diagnosis" (54), "explained" (49), "empathy" (44), "consent" (25). Analysis: students proposed concrete communication moves: warn → name → pause & check; allow silence; invite questions; ensure informed consent and documentation.
- **Scene 3 — Actionable empathy.** Top terms: "patient" (123), "patients" (72), "empathetic" (55), "empathy" (29), "care" (22), "communication" (14). Analysis: reflections shifted to first-person commitments: warm greeting, using names, eye-level seating, brief emotional check-ins, closing instruction loops.

Progression across scenes. The class moved from constraints (Scene 1) → technique (Scene 2) →

commitments (Scene 3), the intended instructional arc.

Post-session feedback (n = 145).

- Enjoyable/very enjoyable: 94%
- Prefer films for empathy/communication learning: 89%
- Strongly recommend continuing such sessions: 92%
- Reported enhanced understanding of empathy: 88%

Discussion

A single AETCOM hour, built on a scene-prompt–debrief spine, produced an observable discursive shift toward concrete, ethically coupled behaviours. This resonates with published accounts of using films to teach professionalism, ethics, and communication—domains where affect and reflection are essential to learning.[4,5,7,8]

Films provide emotionally credible, consequence-rich scenarios without exposing real patients, creating a safe space for perspective-taking and practice with language. Learners can rehearse "moves" (warn → name → pause & check) that map directly onto NMC's AETCOM expectations for communication and consent.[1–3,9,10] Beyond professionalism, empathy links to adherence and clinical outcomes in observational work, strengthening the case for early, deliberate pedagogy rather than leaving empathy to the hidden curriculum.[6]

The intervention fit within routine time, required only a lawful film copy, and used prompts/debriefs that any instructor can adopt with minimal preparation—factors that matter for wide AETCOM implementation.[1–3,9,10]

Limitations:

- This was a Single-institution study. Findings may not generalize beyond this setting.
- Design was descriptive. There was no comparison group or inferential statistics, so, causality cannot be inferred.
- Word-frequency analysis is a signal and not saturation. Counts indicate salience but do not replace rigorous thematic coding.

Conclusion

Within routine AETCOM time, a compact cinemeducation session elicited strong student endorsement and a clear movement from "we lack time" to "here's what I will try tomorrow." In an NMC framework that places attitude, ethics, and communication at the centre of the Indian Medical Graduate's roles, this is a practical, low-cost way to help students translate compassion from cinema to clinic.[1–3,10]

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Review Article

SRHU MEDICAL JOURNAL

3D Bioprinting: Emerging Paradigms in Repair, Regeneration, and Microarchitectural Remodelling

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In the field of regenerative medicine three-dimensional (3D) bioprinting emerging as transformative technology focusing on science of biomaterials, cell development, and additive manufacturing to fabricate functional tissues and organs. Wide range of combinations as bioinks composed of living cells, biomaterials, and growth factors, used to design the precise, layer-by-layer deposition mimics the native tissue architecture. Although the recent advances in in situ bioprinting have expanded applications in wound healing and localized repair. However, clinical translation remains limited by challenges such as inadequate vascularization, mechanical instability, bioink variability, and scalability. Ongoing innovations—including multi-material printing, dynamic crosslinking, computer-aided design, and artificial intelligence integration—are enhancing construct fidelity and functionality. This review highlights current progress, biomedical applications, and future directions, with emphasis on strategies to achieve clinically viable, patient-specific tissue and organ replacements.

Keywords: 3D bioprinting, bioink, regenerative medicine, tissue engineering, organ fabrication

Introduction

Over the past few decades, tissue engineering and regenerative medicine (TERM) have emerged as dynamic, interdisciplinary fields, making significant contributions to the development of engineered constructs for a variety of tissues, including skin, bone, cartilage, liver, heart, neural, and vascular systems [1,2]. The clinical demand for such constructs is substantial, driven by a global shortage of donor organs and the limitations associated with conventional grafts and implants. Reflecting this need, the bioengineered graft and implant market is projected to grow at a compound annual growth rate (CAGR) of 14.3% between 2025 and 2030, underscoring both the biomedical and commercial potential of these technologies.

Within this evolving landscape, 3D bioprinting has emerged as a transformative technology, enabling precise, layer-by-layer deposition of cells, biomaterials, and bioactive molecules to fabricate complex, functional tissues. This approach integrates principles of additive manufacturing, biomaterials science, and cellular biology to closely mimic the structural and functional organization of native tissues. The origins of 3D bioprinting can be traced to foundational advances in additive manufacturing. In 1984, Charles Hull patented stereolithography, establishing the foundation for rapid prototyping and additive manufacturing [3,4]. The first commercial 3D printer, the SLA-250, was introduced in 1988, followed by the coining of the term "3D printer" by Emmanuel Sachs in the 1990s, which enabled fabrication of diverse materials including plastics, metals, and ceramics [5]. By the mid-1990s, additive manufacturing transitioned into the biomedical domain, exemplified by the first applications of biomaterials in tissue regeneration. Between 2001 and 2004, advances such as bladder-shaped polymer scaffolds seeded with donor cells, high-viability inkjet-based bioprinting, and scaffold-free tissue printing marked critical milestones in the field [6,7].

Cite this article as: Rauthan P., Santhanam A., and Dhasmana A., 3D Bioprinting: Emerging Paradigms in Repair, Regeneration, and Microarchitectural Remodelling. SRHUMJ. 2024;2(2);

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Manuscript received: 18.08.24; Revision accepted: 20.10.24

The introduction of bioprinters like the Novogen MMX in 2009 accelerated commercialization and clinical translation efforts [8,9]. Over the following decade, bioprinting achieved major breakthroughs, including scaffold-free vascular constructs (2009), bioprinted skin and hepatocyte-laden collagen matrices (2010), cartilage and liver tissues (2012), integration of vascularized constructs with circulatory systems (2014), and the fabrication of bioprinted heart valves (2016). Currently, the most widely produced tissues include vascular, cardiac, hepatic, osteogenic, and dermal constructs, highlighting the versatility and growing clinical relevance of 3D bioprinting [10,11].

Contemporary bioprinting research continues to focus on optimizing printing methodologies rather than large-scale commercialization. Three principal modalities—laser-assisted, inkjet-based, and extrusion-based printing—have been developed, each requiring tailored bioinks to balance cell viability, mechanical stability, and print fidelity [12]. Laser-assisted bioprinting offers high precision but poses thermal risks to sensitive cells, whereas inkjet and extrusion approaches provide low shear stress environments compatible with diverse cell types, making them suitable for clinical applications. Experimental applications such as the bioprinted bionic pancreas illustrate both the potential and current challenges of translating complex soft tissues into clinical use. Bioprinting enables precise spatial placement of pancreatic islets within porous scaffolds, improving nutrient diffusion, vascularization, and cell–cell interactions [13]. However, significant challenges remain, including development of ECM-mimicking bioinks, maintaining mechanical stability, and overcoming printer resolution limitations (~100 μm) that impede vascular integration [14]. While tissues like skin, liver, and cardiac constructs have advanced toward clinical implementation, the bionic pancreas remains at an early stage, with success contingent upon improvements in bioink design, vascularization strategies, and high-resolution printing technologies.

In conclusion, 3D bioprinting represents a paradigm shift in TERM, offering patient-specific, scalable, and functional tissue constructs. Continued advances in imaging, bioink engineering, and automated bioprinting platforms are essential to translate laboratory innovations into clinically viable solutions, addressing organ shortages and redefining therapeutic strategies in regenerative medicine [15].

Table 1: Advances of Bioprinting in organ/tissue culture and their impact regeneration/repair

Skin substitutes	Developed for wound healing and the study of skin infection pathophysiology
Blood vessels	Emphasizing geometric optimization, flow dynamics, and molecular diffusion
Heart valves	Utilizing hydrogels and valve interstitial cells (VICs) for high-efficiency constructs
Bone tissue	Focusing on scaffold architecture, pore geometry, cellular viability, and mechanical integrity
Liver tissue	Drug testing and toxicological screening of chemical compounds;

State of the Art: Designing and Printing Strategies:

The recent advancement of the Modern 3D bioprinting integrates patient-specific design, optimized biomaterials, and biologically relevant printing techniques. computer-aided design (CAD) and medical imaging (CT, MRI) generate blueprints for constructs, with soft tissue designs requiring calibration for post-printing fusion and shrinkage [16]. Key printing modalities include: *Inkjet*: High resolution and speed; limited to low-viscosity bioinks; *Extrusion*: Supports viscous hydrogels and multi-materials; widely used but may reduce cell viability due to shear stress; *Laser-assisted*: Enables precise deposition of dense cell suspensions; risk of thermal damage [17]. Emerging techniques like freeform reversible embedding allow printing of soft inks within sacrificial baths. Bioprinting strategies are either: Scaffold-based: Focused on mechanical integrity and nutrient diffusion, and Scaffold-free: Use fusogenic cell spheroids to mimic natural tissue fusion [18].

In situ bioprinting enables direct deposition at wound sites, demonstrated in skin regeneration using handheld or robotic systems. Post-processing is crucial for maintaining the viability of thick, bioprinted tissues. This stage relies heavily on perfusion bioreactors and needle-based irrigation systems, which temporarily supply nutrients and oxygen until a functional vascular network develops. Advanced systems are being designed with detachable porous needles and pressure-controlled drip mechanisms to support perfusion, enable sterile handling, and provide dynamic biomechanical conditioning that accelerates tissue maturation [19]. On the commercial front, platforms such as the BioAssembly Tool (Sciperio/nScript Inc., USA) and Bioplotter (Envisiontech) have advanced

clinical translation by enabling 3D bioprinting of living tissues using combinations of cells and hydrogels [20]. Collaborations with companies like Neatco (Canada) have also led to the development of simple robotic bioprinters. A key direction in the field is the rise of personal fabricators—desktop rapid prototyping devices akin to personal computers [21]. A group at Cornell University designed one of the first affordable, easy-to-assemble systems, demonstrating its application in cartilage tissue engineering. With mass production, costs could fall to as low as US$250, potentially democratizing access to organ printing technologies.

Despite progress, major challenges remain, particularly in achieving vascularization, reducing bioink costs, and reaching sub-100 µm resolution needed for complex organ fabrication. Thus, for addressing these issues will require continued innovation in bioreactor design, biofabrication systems, and mechanical engineering integration (Fig.1).

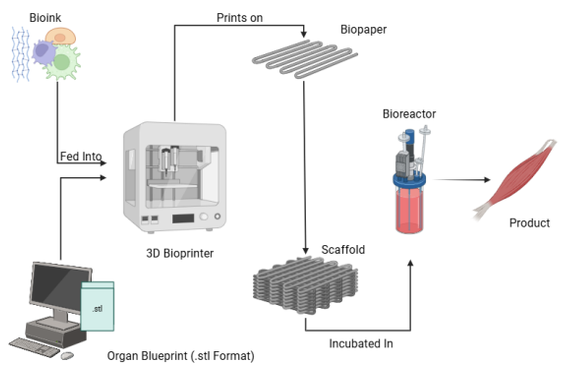

Figure 1 Schematic representation 3D Bioprinting procedure.

- **Organ Blueprint and Biopaper in 3D Organ Printing**

The concept of an "organ blueprint" represents a software-based computer program that provides detailed instructions for the layer-by-layer deposition of biological components via a dispensing device, based on a CAD file. In practice, this often involves bioprinter-compatible stereolithography (STL) files, which guide the precise architecture of the printed construct [9,22]. A major challenge in blueprint design is the post-processing behavior of soft tissues, which undergo fusion, retraction, compaction, and remodeling after printing. Consequently, organ blueprints typically require scaling adjustments and shape modifications to compensate for these changes, ensuring that the final matured construct conforms to the desired anatomical dimensions. To address this, tissue compaction, retraction, and remodeling coefficients must be empirically determined and integrated into CAD models. Unlike solid scaffolds, which can be directly modeled from 3D clinical imaging data, soft-tissue blueprints cannot be automatically generated due to the inherent dynamic remodeling of living tissues during maturation [23].

A second critical element in organ printing is biopaper, defined as processable, biomimetic, and tissue-fusion–permissive hydrogels specifically engineered to serve as extracellular matrices during the bioprinting process. Biopaper provides the necessary structural support, cell adhesion sites, and biochemical cues to facilitate tissue formation. A recent comprehensive review highlighted the role of hydrogels as extracellular matrices for organ printing, underscoring their importance in supporting cell viability and function [24]. The development of functionalized hydrogels, such as biomimetic photosensitive matrices incorporating RGD peptides, has significantly improved the survival and integration of printed tissue constructs. The design and synthesis of processible, biomimetic hydrogels (biopaper) thus remain one of the most critical and challenging aspects of organ-printing technology [25]. This area offers a unique opportunity for chemical engineers to apply their expertise in polymer chemistry, biomaterials design, and photopolymerization to create novel extracellular matrix analogs that can both mimic native tissue environments and withstand the mechanical and biological demands of bioprinting.

- **Bio-inks**

Bioinks are central to the success of 3D bioprinting, combining cells, biomaterials, and biochemical factors to create functional constructs. An ideal bioink must achieve a balance between printability, biocompatibility, and mechanical integrity while preserving cell viability. The architecture of the engineered graft is largely dictated by the choice of bioink, which directly influences tissue fusion, maturation, and the biomimetic fidelity of the printed organ. Inspired by embryonic tissue fusion, organ printing often relies on self-assembled spheroids with viscoelastic and fusogenic properties [26] Although small-scale spheroid production using methods such as shaking, centrifugation, extrusion, or non-adhesive substrates is well established, scaling this process for standardized robotic dispensing remains a significant challenge, alongside the design of bioink cartridges [11].

Polymeric Bioinks. Wide range of biopolymers used to print the 3D microarchitecture to mimic the native tissue. Natural polymers such as collagen, gelatin,

alginate, fibrin, and hyaluronic acid provide extracellular matrix (ECM)-like cues that support adhesion and proliferation. Gelatin methacryloyl (GelMA), a photopolymerizable hydrogel, has been widely used in cardiac and neural constructs, while fibrin and collagen promote angiogenesis and neurogenesis in skin and nerve regeneration [14]. However, their weak mechanical stability necessitates reinforcement. Synthetic polymers
such as polyethylene glycol (PEG), polycaprolactone (PCL), and polylactic acid (PLA) offer tunable mechanics and degradation rates but lack bioactivity unless functionalized with peptides such as RGD groups [27].

Composite Bioinks. Composite systems combine natural and synthetic polymers or inorganic fillers to enhance both biofunctionality and mechanical stability. Examples include alginate–collagen blends for improved fidelity and adhesion, and hydrogel–ceramic composites such as hydroxyapatite and bioactive glass for osteoconductive applications. Recent advances such as nanoengineered ionic–covalent entanglement (NICE) bioinks have produced resilient bone-like constructs with enhanced mechanical strength [28].

Cell-Seeded Bioinks. Cell-seeded formulations incorporate living cells or spheroids to promote tissue-specific maturation. MSCs, iPSCs, and differentiated cells such as hepatocytes or cardiomyocytes are widely applied. Co-printing iPSC-derived cardiomyocytes with endothelial cells has yielded vascularized cardiac tissues [29]. For skin bioprinting, keratinocytes remain a major cell source due to their proliferative capacity and resistance to senescence, though challenges such as long expansion times and hypertrophic scarring persist [30].

Hybrid Bioinks. Hybrid formulations integrate polymers, cells, and functional additives such as growth factors, nanoparticles, or decellularized extracellular matrix (dECM). dECM-based inks preserve native biochemical cues and have demonstrated success in liver and cardiac models. Nanoparticles like nanoclay or hydroxyapatite improve mechanics, conductivity, and controlled release [28]. Emerging in situ applications include pore-forming hybrid inks used in handheld extruders for wound repair, enabling simultaneous mechanical support and accelerated healing [30].

Application of 3D printing

3D bioprinting leverages additive manufacturing to create tissue constructs from bioinks containing living cells (Table2). Cytocompatible hydrogels are deposited layer by layer under guidance from CAD files, replicating native tissue architecture [9].

Table 2: Summary table of studies of 3D printed grafts: composition, methodology and outcomes

Organ	Tissue	Methodology	Bioink composition	Pros	Cons
Skin	Whole skin (Multilayer)	Computer-controlled 3D printer	Bioinks composed of viable cells, biomaterials	Provides suitable environment for cell migration, differentiation	-
	Outer layers	Ex vivo (inkjet-, extrusion-, laser-based bioprinting)	Human fibroblasts, human plasma, calcium chloride	High degree of precision and resolution	Lower cellular viability
	Outer layers	In situ bioprinting	Bioink composed of fibroblasts, collagen I, and fibrinogen	Allows for biomaterials to be printed directly into or onto the target/organ	Do not stimulate regeneration of vasculature, nerves, sweat and sebaceous glands
Heart	Cardiac and microvascular tissue	Inkjet bioprinting	Gelatin methacryloyl, heart extracellular matrix hydrogel	Compatible with many biomaterials and maintain remarkable cell viability	Cannot print at high density

		Extrusion printing	Alginate, PEG, fibrinogen	Permits faster, simpler, and more affordable bioprinting	Dispensing pressure and shear stress results in poor cell survival
		Freeform reversible embedding printing	Collagen hydrogels	Overcome the limitations of printing soft and low viscosity bioinks.	Risk of loosing viability of cells
Kidney	Parenchymal tissue	Extrusion-based bioprinting	Hydrogels, akginate, PEG	High precision and widely used in industry	Cannot handle high pressure
		Droplet-based bioprinting	Gelatin methacrylol (GelMA), collagen, poly (ethylene glycol) (PEG)	Affordable, ideal for feasibility studies	Thermal and mechanical on cells, expensive
Neurons	Neural tissue Cortical NSCs	Micro-extrusion-based bioprinting	Alginate, carboxymethyl chitosan and agarose	Ability to use high viscosity	Distortion of cell structure
		Inkjet bioprinting	Collagen and fibrin	High speed, availability, low cost	High speed, availability, low cost
Liver	Hepatic cells	Extrusion based bioprinting	Alginate, collagen	Materials with a wide range of viscosities can be constructed efficiently	Low resolution of scaffolds
Bone	All bone tissue	3Dimensional printing	nanoengineered ionic covalent entanglement (NICE) bioink	3d printing using NICE bioink provides mechanically resilient, cellularized structures	NICE bioink is costly so it makes the whole process costly

Traditional scaffold-based methods support cell adhesion and differentiation but are limited by imprecise cell placement, poor vascularization, and labor-intensive assembly [11,13]. Automated bioprinting overcomes these challenges, enabling precise deposition of cells and biomaterials, improving construct fidelity, functionality, and scalability.

Composite Organ Printing integrates diverse cell types, biomaterials, and structural elements to mimic the complexity of native organs. The process typically involves three stages: pre-processing (imaging, model design, bioink formulation), printing (layer-by-layer deposition), and post-processing (maturation in bioreactors) [23]. High-resolution imaging tools such as CT and MRI are essential for accurate 3D model reconstruction, though challenges remain in color capture for skin reconstruction and radiation risks associated with CT [18,31]. Notably, successful fabrication of layered skin constructs at Hannover Medical School and Laser Zentrum Hannover underscores its translational potential. Laser-assisted bioprinting (LaBP) has emerged as a valuable modality for composite organ printing, enabling high-resolution placement of multiple cell types and bioinks of varying viscosities [32].

Organoids and 3D Models produced via bioprinting offer physiologically relevant platforms for studying development, disease progression, and therapeutic responses. Unlike conventional 2D cultures, bioprinted organoids recreate native cell–cell and cell–matrix interactions within a 3D microenvironment [33,34]. Using stem cell-laden bioinks, self-organizing constructs resembling liver lobules, kidney nephrons,

neural spheroids, and intestinal crypts have been generated, supporting applications in disease modeling, drug screening, and regenerative medicine. For instance, liver organoids printed with alginate–collagen bioinks have provided superior predictive capacity in drug metabolism studies compared to standard in vitro assays [35]. However, challenges persist in vascularization, scalability, and functional integration. Emerging strategies coupling bioprinting with organ-on-chip systems show promise in enabling dynamic perfusion and long-term maturation [36]. Future progress will depend on incorporating vascular networks, immune cells, and multi-tissue interfaces to enhance physiological relevance.

In Situ Tissue Remodeling and Vascular Engineering: ***F***urther extend the applications of bioprinting. Vascular graft fabrication relies on selecting appropriate cell types, scaffold materials, and biochemical or mechanical stimuli to induce remodelling in vitro (Figure 2). While endothelial cells (ECs) and smooth muscle cells (SMCs) have been widely used since the 1980s, limited growth capacity has prompted exploration of stem cell–based approaches. Autologous cells remain the preferred option to minimize immunogenicity [37]. Both cellular and acellular grafts are under investigation, with the latter designed to promote host-driven regeneration by tailoring structural, chemical, and degradable features. Preclinical studies highlight the potential of mesenchymal stem cells (MSCs), muscle-derived stem cells (MDSCs), and pericytes to enhance patency and remodeling [38,39]. Nonetheless, evidence indicates that host-derived cells ultimately dominate long-term graft integration. Clinical advances, such as mononuclear cell–seeded biodegradable scaffolds applied in Japan [40,41] and ongoing U.S. trials for congenital cardiac disease [42], demonstrate the translational momentum of these strategies.

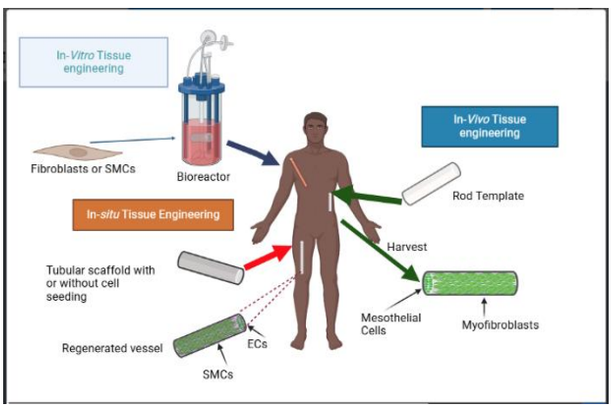

Figure 2: Illustration of In-Situ and In-Vivo Tissue Engineering Respectively

Advancement and future prospective

The rapid advancement of 3D bioprinting is driven by technological innovation and cross-disciplinary integration, with future progress requiring the convergence of computational design, translational biology, and high-throughput manufacturing. CAD and computer-aided manufacturing (CAM) are essential for converting medical imaging data into anatomically accurate 3D constructs, while advanced algorithms and artificial intelligence (AI) now enable optimization of print parameters, prediction of cell viability under shear stress, and the creation of complex vascular networks. Such computationally guided, predictive blueprints are increasingly applied in fields like cardiac tissue engineering, where spatially optimized deposition of endothelial and myocardial cells mimics physiological architecture [43]. Equally critical is translational biology, which addresses challenges in cell sourcing, immunocompatibility, and functional maturation. Autologous stem cells, including mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs), minimize immune rejection and support patient-specific therapies, while decellularized extracellular matrix (dECM)-based bioinks provide biochemical cues that enhance differentiation and maturation. In situ bioprinting exemplifies clinical potential, as handheld devices have enabled direct fibroblast- and collagen-based deposition into wound sites, although scaling from animal models to human applications still requires rigorous preclinical validation and compliance with Good Manufacturing Practices (GMP) [44].

Alongside these biological advances, the development of high-throughput, GMP-compliant bioprinting platforms with multi-nozzle and automated capabilities is essential for reproducibility and scalability. Innovations such as freeform reversible embedding and high-precision extrusion are driving improvements, while industrial collaborations with companies including Organovo, EnvisionTEC, and Rokit are accelerating applications in skin, liver, and vascular models for pharmaceutical testing and regenerative therapies [45]. Ultimately, the future of 3D bioprinting will depend on the integration of cost-effective, standardized bioinks—particularly ECM-derived hydrogels from donor tissues—with scalable manufacturing systems to enable on-demand, patient-specific graft fabrication and reduce reliance on organ donation.

In brief, 3D bioprinting is redefining tissue engineering and regenerative medicine by integrating additive manufacturing, biomaterials, and cell biology. Applications now include skin grafts, vascular conduits, liver lobules, and cardiac patches, yet clinical

translation is limited by challenges such as vascularization, mechanical instability, high bioink costs, and regulatory barriers. Advances in computer-aided design, translational biology, and scalable bioprinting systems are addressing these gaps, while emerging strategies—such as 4D bioprinting, AI-assisted design, and in situ printing—offer new possibilities for personalized and real-time therapies [46]. Although still evolving, 3D bioprinting holds immense promise to overcome organ shortages, improve drug testing, and enable on-demand tissue fabrication, making it a cornerstone of future regenerative medicine.

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