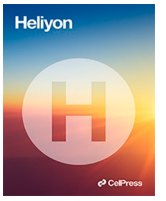
Heliyon 10 (2024) e40596

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Exploring nanotechnology solutions for improved outcomes in gastrointestinal stromal tumors

Sofia Gabellone [a], Silvia Vanni [a,*], Valentina Fausti [b], Giacomo Miserocchi [a], Chiara Liverani [a], Chiara Spadazzi [a], Claudia Cocchi [a], Chiara Calabrese [a], Davide Cavaliere [c], Carlo Alberto Pacilio [c], Giorgio Ercolani [c], Federica Pieri [d], Lorena Gurrieri [b], Nada Riva [b], Robin Jones [e], Alessandro De Vita [a]

[a] *Preclinic and Osteoncology Unit, Biosciences Laboratory, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", 47014, Meldola, Italy*
[b] *Clinical and Experimental Oncology, Immunotherapy, Rare Cancers and Biological Resource Center, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", 47014, Meldola, Italy*
[c] *General and Oncologic Surgery, "Morgagni-Pierantoni" Hospital, 47121, Forlì, Italy*
[d] *Pathology Unit, "Morgagni-Pierantoni" Hospital, 47121, Forlì, Italy*
[e] *Sarcoma Unit, The Royal Marsden NHS Foundation Trust, SW3 6JJ, London, UK*

A R T I C L E I N F O

Keywords:
GIST
c-Kit
DOG1
Imatinib
TKI inhibitors
Nanotechnology

A B S T R A C T

Objectives: Gastrointestinal stromal tumors, the most prevalent mesenchymal tumors (80 %) of the gastrointestinal tract, comprise less than 1 % of all gastrointestinal neoplasms and about 5 % of all sarcomas. Despite their rarity, Gastrointestinal stromal tumors present diverse clinical manifestations, anatomic locations, histological subtypes, and prognostic outcomes.
Methods: This scoping review comprehensively explores the epidemiology, clinical characteristics, diagnostic and prognostic modalities, as well as new therapeutic options for Gastrointestinal stromal tumors.
Results: A particular focus is placed on the promising role of bio-nanomaterials as multifunctional agents for drug delivery and 3D tumor microenvironment modeling. Bio-nanomaterials offer promising opportunities for targeted drug delivery, overcoming treatment resistance, and improving therapeutic efficacy.
Conclusion: Despite significant advancements, Gastrointestinal stromal tumors remain a complex clinical entity with ongoing challenges. The integration of nanotechnology into Gastrointestinal stromal tumors management offers the potential to enhance patient outcomes. Future studies should prioritize the development and evaluation of nanomaterial-based therapies in clinical trials to facilitate the translation of laboratory discoveries into real-world clinical applications.

Abbreviations: CNT, carbon nanotube; CTC, circulating tumor cell; CT, contrast-enhanced; dECM, decellularized extracellular matrix; ECM, extracellular matrix; GIST, gastrointestinal stromal tumor; VEGFR, growth factor receptor; ICC, interstitial cell of Cajal; Ng, nanogel; NP, Nanoparticle; OS, overall survival; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; PLGA, poly lactic-co-glycolic acid; sPLA2, secretory phospholipase A2; STS, soft tissue sarcomas; SCF, stem cell factor; TKI, tyrosine kinase inhibitor; TEP, tumor-educated platelet; TME, tumor microenvironment.

* Corresponding author. Preclinic and Osteoncology Unit, Biosciences Laboratory, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Via P. Maroncelli 40, 47014, Meldola, Italy.
E-mail address: silvia.vanni@irst.emr.it (S. Vanni).

https://doi.org/10.1016/j.heliyon.2024.e40596
Received 21 November 2023; Received in revised form 19 November 2024; Accepted 20 November 2024
Available online 22 November 2024

1. Introduction

Soft tissue sarcomas (STS) are a heterogeneous group of mesenchymal neoplasms with over 100 different histologic subtypes [1]. Gastrointestinal stromal tumor (GIST) is the most common mesenchymal malignancy (soft tissue sarcoma subtype) affecting the gastrointestinal tract [2]. While GISTs are classified as sarcomas, their distinct histogenesis, clinical features, and treatment necessitate separate considerations [2,3]. GISTs originate from the interstitial cells of Cajal (ICCs) [4]. Their incidence is estimated in 80 % of non-epithelial or mesenchymal tumors, and in 5 % of all sarcomas. The overall incidence of GISTs in the last decade was 0.70 per 100, 000 people per year [5]. GISTs mainly arise in the stomach (55.6 %), followed by the small bowel (31.8 %), colorectum (6 %), other locations (5.5 %) and the esophagus (0.7 %) [3,4]. In regard to age at diagnosis, its range varied from the sixth and seventh decade of life, and approximately 0.4–2 % in children and young adults under the age of 20 years [6] with equal distribution of males and females [rate ratio (RR), 1.35], non-Hispanics than Hispanics (RR, 1.23), and blacks (RR, 2.07) or Asians/Pacific Islanders (RR, 1.50) than whites [6,7]. c-kit (CD117) and anoctamin1 (DOG1) emerged as the most specific and sensitive biomarkers for these neoplasms, and their expression is immunohistochemically detected in >95 % of GISTs [8]. GISTs are driven by mutations in the c-KIT or PDGFR-α genes. Approximately 80 % have c-KIT mutations, while 8–10 % have PDGFR-α mutations. Approximately 15 % of GISTs do not have a detectable mutation in either KIT or PDGFRA. In other respects, these so-called 'wild-type' GISTs are clinically indistinguishable from KIT- or PDGFRA-mutant GISTs. GISTs occur in different parts of the GI tract and show a histological spectrum. Although spindle-cell morphology predominates, tumors with epithelioid or pleomorphic cell features also occur (70 %) [9]. Other subtypes such as epithelioid cells and mixed spindle and epithelioid cells account for 20 % and 10 % of GISTs, respectively. The current NCNN, ESMO, and EURACAN guidelines identified mitotic rate, tumor size, and tumor site as the three primary prognostic variables. Tumor rupture is regarded as an independent risk factor [10]. Imatinib mesylate, a selective tyrosine kinase inhibitor (TKI), improves clinical outcomes in GIST as both advanced metastatic disease therapy and postsurgical adjuvant treatment [11]. Sunitinib, a multi-targeted tyrosine kinase inhibitor (TKI) with anti-tumor and anti-angiogenic properties, was approved in 2006 for patients with GISTs. Its mechanism of action involves inhibiting multiple receptor tyrosine kinases, including vascular endothelial growth factor receptors (VEGFRs) 1–3, platelet-derived growth factor receptors (PDGFRs) α and β, KIT, colony-stimulating factor receptor 1, RET and FLT3 [12]. However, the development of drug resistance and the challenges of managing advanced disease underscore the need for continued research. Subsequent therapies like sunitinib and regorafenib have expanded treatment options, but the complexity of GIST necessitates ongoing exploration of new treatment approaches. In this review we discuss the use of nanotechnology as a promising avenue for addressing the limitations of traditional cancer treatments. By encapsulating drugs within nanoparticles, researchers can enhance drug delivery, target specific tumors, and reduce side effects. Various nanoparticle types, including those derived from metals, polymers, and lipids, are being investigated for their potential in treating GISTs. Additionally, nanotechnology is contributing to improved diagnostic tools and a deeper understanding of tumor biology through three-dimensional cell culture models. While significant progress has been made in GIST management, ongoing research is essential to develop more effective and personalized treatments. By combining advancements in nanotechnology with a comprehensive understanding of GIST biology, the medical community can work towards improving patient outcomes and ultimately achieving a cure [13].

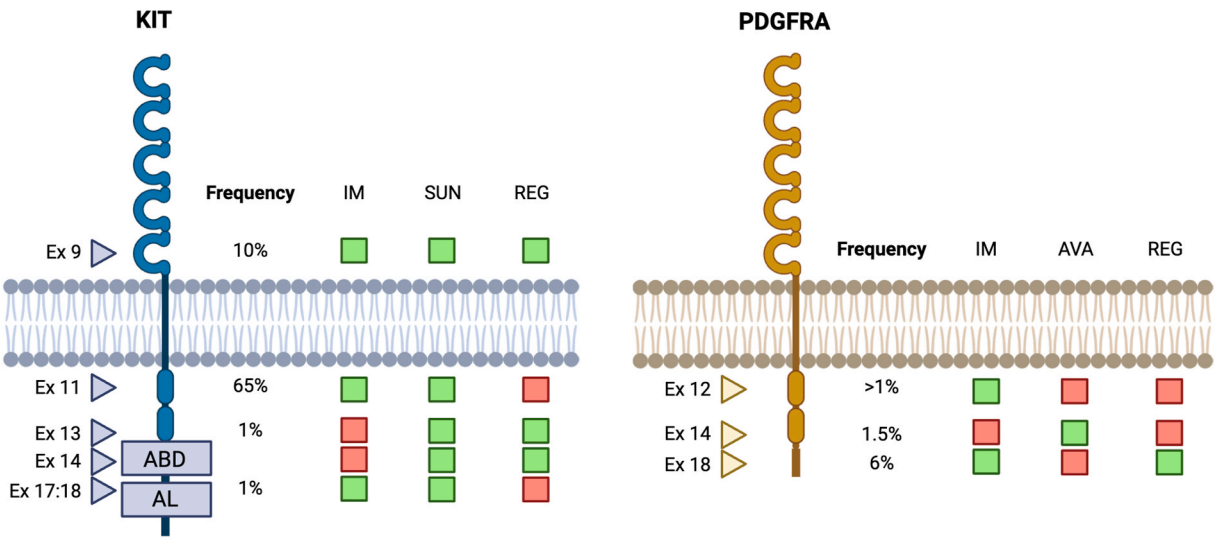


Fig. 1. Sensitivity of KIT and PDGFRA mutations to approved TKIs. Green: sensitive, red: resistant; IM:imatinib; SUN:sunitinib; REG: regorafenib; AVA: avapritinib; ABD: ATP-binding domain; AL: activation loop. Frequency of mutations affecting exons of KIT and PDGFRA are indicated in brackets. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

2. Etiopathogenesis

2.1. Histology

GISTs are characterized by three histological types according to cellular morphology: spindle cells (77 %), epithelioid cells (8 %), mixed spindle and epithelioid cells (15 %) [14]. The cytologic profile of GISTs is monomorphic, characterized by rounded to elongated nuclei with sufficient chromatin and inconspicuous nucleoli [15]. Other histological features are represented by paranuclear vacuoles, extensive nuclear palisading mimicking schwannoma, prominent neuroendocrine-like features mimicking paraganglioma, signet-ring cytomorphology [16,17] marked lymphocytic infiltration [18] and hyaline eosinophilic cytoplasmic structures [19], which are predominantly identified in small intestinal GISTs. The typical size of GISTs tumor is from less than 10 mm to very large lesions measuring more than 350 mm [20]. GISTs are located on the bowel wall, mucosa, outwards the bowel wall, or have a dumbbell configuration with both mucosal and serosal based masses [21].

2.2. Genomic alterations

GISTs are characterized by activating mutations in the type III tyrosine kinase receptors as c-KIT and PDGFRa genes (Fig. 1) [16, 22]. Genetic analysis of GISTs show that 60–85 % present mutations in the c-KIT gene, while 5–10 % have mutations in the PDGFRa gene. Approximately 10–15 % of GISTs do not have detectable mutations in any of these receptors (wild type), suggesting that other molecular pathways can also be involved in the pathogenesis of these tumors [23]. c-KIT is implicated in the growth and maintenance of erythrocytes, mast cells, melanocytes, germ cells and interstitial cells of Cajal (ICC) [24]. The intracellular kinase domain is characterized by the presence of the ligand Stem Cell Factor (SCF) [4], which causes dimerization and autophosphorylation through the phosphorylation of tyrosine residues [25]. The active form of c-KIT, phosphorylates downstream signaling proteins, affecting cell proliferation, chemotaxis, and apoptosis [26]. c-KIT exons involved in GISTs are 11, 9 and exons 13, 17, 18. Exon 11 is the most frequently mutated region with in-frame deletions of codons 557 and 558 [17]. Mutations in c-KIT exon 9 occur in c.a 8–10 % of GISTs and are associated with small or large bowel tumors, while primary mutations in exons 13, 17 and 18 are rare [27]. PDGFRa-mutant occurs in 10 % of GIST, generally arises in the stomach [28] and involves exon 18 (8 %), 12 and exon 14 [28]. Mutations in c-KIT or PDGFRa play essential roles in the upregulation of downstream signaling pathways, including RAS/RAF/MAPK and PI3K/AKT/mTO [28,29]. Wild type GISTs are classified into two diverse groups i) succinate dehydrogenase (SDH) deficient group and ii) non-SDH deficient group [30]. SDH is a complex consisting of four subunits (SDHA, SDHB, SDHC and SDHD) located in the mitochondria, and involved in the tricarboxylic acid cycle and electron transport chain. Mutations in SDH arise in young adults. These mutations are associated with the accumulation of succinate which promote upregulation of HIF1α and inhibition of DNA demethylation. Non-SDH deficient groups include neurofibromatosis type 1 (NF1) and GISTs with BRAF, KRAS, PIK3CA mutations and fusion genes [30]. GISTs

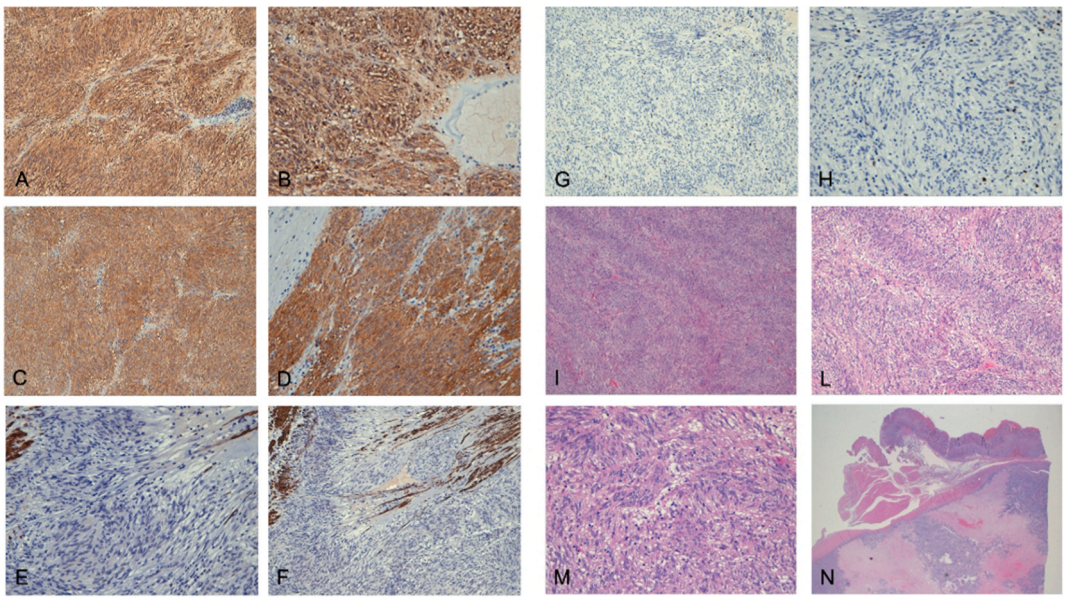


Fig. 2. Examples of gastrointestinal stromal tumor (GIST) morphology. Microscopic picture. (A–B) 10×, 20 × objective magnification of GIST that stains c-kit positive; (C–D) 10×, 20 × objective magnification of GIST that stains DOG-1 positive; (E–F) 10×, 20 × objective magnification of GIST that stains desmin positive; (G–H) 10×, 20 × objective magnification of GIST that stains ki67 positive. Microscopic picture, H&E stain. 5, 10×, 20 × objective magnification image of a GIST (I–M). Microscopic pictureH&E stain. 4 × represents an objective magnification of normal gastric mucosa with intraluminal growth of the tumor (N).

are characterized by chromosomal instability. Frequent changes observed in all GIST groups included losses in chromosome arms 1p (51 %), 14q (74 %), and 22q (53 %). Metastatic GISTs are characterized by higher-level amplifications at 8q and 17q (57 and 43 %) than benign GISTs (8 and 0 %; P = 0.001) and malignant primary GISTs (33 and 25 %; P = 0.05). Gains and high-level amplifications at 20q are only in malignant primary and metastatic GISTs (P = 0.01) but gains at 5p are not found in benign GISTs (P = 0.01) [31]. Losses in chromosomal arm 9p are more common in metastatic GISTs than in initial malignant GISTs (63 and 36 %; P = 0.05). Losses in 13q are less common in benign GISTs than in malignant GISTs [32].

3. Diagnosis

3.1. Molecular landscape

GIST diagnosis involves both immunohistochemistry and molecular analysis. GISTs are typically positive for the CD117 antigen, a marker of KIT receptor tyrosine kinase expressed by interstitial cells of Cajal (ICC) [33]. Despite its high prevalence in GISTs (95 %), c-KIT expression is not a specific diagnostic marker due to its presence in other mesenchymal tumors. DOG1 is considered a sensitive and specific marker of GISTs regardless of CD117 expression. DOG1 is also independent of KIT or platelet-derived growth factor receptor α (PDGFRA) mutation status in GISTs [34]. Staining of GISTs for other standard laboratory immunomarkers is more variable, including CD34 (70 %), smooth-muscle actin (35 %), S-100 (10 %) and desmin (≈5 %) (Fig. 2E–F) (Table 1) [14]. Again, Ki67 index is an effective predictor of GIST prognosis, particularly for patients with imatinib adjuvant therapy (Fig. 2G–H) [35–37].

3.2. Diagnostic imaging

GISTs exhibit a variety of radiological appearances on imaging studies. Current multimodality imaging approaches include Contrast-enhanced (CT) [38] and magnetic resonance imaging (MRI) [39] (Fig. 3). FDG (18fluoro-deoxy-glucose)-positron emission tomography (PET) scans can provide valuable insights into tumor metabolic activity [40].

Endoscopic ultrasound (EUS) is also used to examine the layered structure, internal echogenicity, size of lesions, and relationship to the extramural structure, providing additional information on malignancy [40,41]. Cold biopsy forceps were used to confirm form and size as well as mass mobility and consistency [40]. Again, EUS-FNA/B is a minimally invasive technique useful to visualize the subepithelial layer, and to reach adjacent organs located in a difficult area [41].

3.3. Liquid biopsy

The gold standard for diagnosing gastrointestinal stromal tumors (GISTs) is a fine needle aspiration biopsy. This procedure offers several advantages over traditional biopsies and is supported by immunohistochemical positivity for c-kit, DOG-1, and CD34. Risk stratification, considering factors such as tumor size, location, and mitotic index, is crucial in the prediction of disease progression and treatment response. Molecular profiling is another key component of GIST management. The most common mutations occur in the KIT (80 %), PDGFRA (10 %), and BRAF, KRAS, PIK3CA, and NF-1 (10 %) genes. While traditional mutation analysis typically relies on tissue samples, this approach can be limited by factors like sample quality, tissue quantity, and the time required for testing. Liquid biopsy, a more recent technique, offers a non-invasive alternative [42], as the analysis of circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), free circulating nucleic acids (DNA, mRNA, non-coding RNA), "tumor-educated platelets" (TEPs), and exosomes. Recent studies compared ctDNA and solid tissue analysis using next-generation sequencing (NGS), demonstrating high concordance rates [43]. Moreover, clinical characteristics such as Ki-67 expression, mitotic count, and tumor diameter have been correlated with the positivity rate of CTCs in liquid biopsies. These findings highlight the potential of ctDNA analysis for monitoring tumor burden and treatment response in GISTs.

4. Prognostic biomarkers in GIST

4.1. Size, high-power field, mitosis

Accurate risk assessment is crucial for managing GISTs. The GEISS guidelines use mitotic activity, tumor size, and location to predict prognosis and inform treatment decisions. These factors are also incorporated in the NIH consensus and Armed Forces Institute of Pathology (AFIP) criteria for GIST risk assessment (Table 2) [44,45].

Table 1
Recommended immunohistochemical markers for gastrointestinal stromal tumors (GIST).

c-KIT	DOG1	c-KIT/DOG1	H-caldesmon	CD34	SMA[a]	Desmin	S-100
95 %	65 %	80 %	60 %	65 %	35 %	1–2%	5 %

[a] SMA, smooth muscle actin.

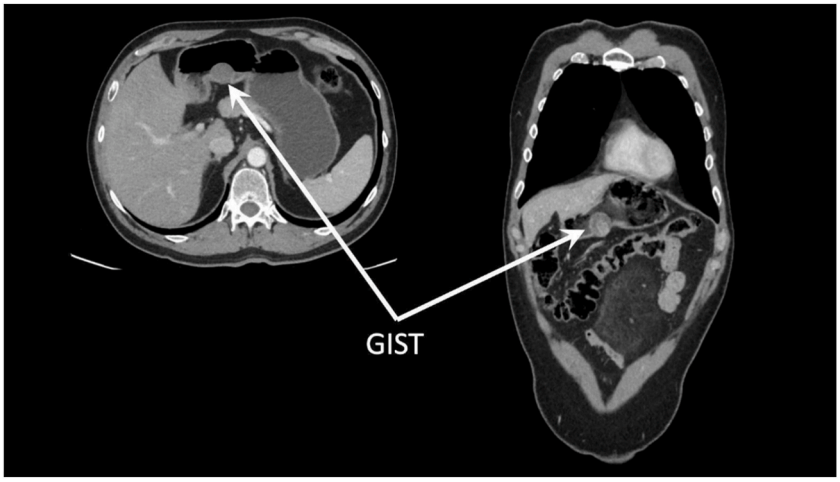


Fig. 3. Representative CT images of gastric GISTs tumor mass (white arrows).

Table 2
Group risk listed by GEIS for GIST adapted from Miettinen et al.

Risk level	Size	Mitotic Index[a]	Location
Very low-risk	2–5 cm	≤5 mitosis	Gastric
Low-risk	>5 y ≤ 10 cm	≤5 mitosis	Gastric
	2–5 cm	≤5 mitosis	Intestinal
Intermediate-risk	>10 cm	≤5 mitosis	Gastric
	>5 y ≤ 10 cm	≤5 mitosis	Intestinal
	2–5 cm	>5 mitosis	Gastric
High-risk intestinal	2–5 cm	>5 mitosis	Intestinal
	>10 cm	≤5 mitosis	Intestinal
	>5 y ≤ 10 cm	>5 mitosis	Gastric
	>10 cm	>5 mitosis	Gastric
	>5 y ≤ 10 cm	>5 mitosis	Intestinal
	>10 cm	>5 mitosis	Intestinal

[a] 50 HPF represents an area of 5 mm^2 in the optical fields used by Miettinen.

4.2. DNA prognostic biomarkers

As previously mentioned, approximately 80 % of GIST patients have activating mutations in c-KIT, while 10 % have mutations in PDGFRa (Fig. 1).

c-KIT exon 11 mutations are associated with higher response rates and longer survival compared to exon 9 mutations in patients from Asia, Europe, and the United States. Both the location of the GIST (stomach) and specific genetic mutations (c-KIT exon 11 deletions) can contribute to more aggressive disease, especially in European patients (KIT delinc557/558; HR 1.45; 95 % CI 1.0–2.2; P = 0.004) [46]. c-KIT exon 9 mutations mainly occur in non-gastric sites and the clinical prognosis is worse than c-KIT exon 11. GIST patients with exon 18 mutations in PDGFRa have lower tumor invasiveness and better OS and RFS (HR 0.23; 95 % CI 0.1–0.6; P = 0.002, 5-year observed survival and relative survival of 84.6 and 89.7 %) [47]. Exon 14 mutations in PDGFRa are relatively common and are generally linked to better clinical outcomes [48]. Patients with PDGFRa mutations or c-KIT exon 11 alterations generally have a positive prognosis after surgical resection, with low rates of recurrence [49]. wt-GIST patients have a poor prognosis and are less responsive to standard therapies [50]. GISTs with SDH deficiency are more common in children (1–2%) and adolescent females [51,52], and they frequently metastasize to lymph nodes. While approximately 15–20 % of GIST patients succumb to metastatic stage, many others survive the progression of the disease. This suggests that SDH-deficient GISTs generally have a more indolent course [53].

4.3. miRNAs and KIT/PDGFRA mutations as circulating biomarkers

Previous research has demonstrated that miRNAs are deregulated in all major cancers and are implicated in tumorigenesis, progression, metastasis, and drug resistance. Since the discovery of microRNAs, they have held great promise for cancer diagnosis, prognosis, and therapy. In GIST, specific miRNA [54,55] expression signatures are associated with chromosome 14q loss [56], anatomical site [57], KIT or PDGFRA mutations [58], tumor risk [59], overall survival [57], and treatment response [60–62]. The overexpression of miR-494 inhibits the expression of c-KIT and its downstream targets phospho-AKT (p-AKT) and phospho-STAT3 (p-STAT3) [63]. MiR-196a expression is associated with high grade tumors and a poor prognosis [57], whereas miR-186 expression

is related to post-operative recurrence [64]. Overexpression of miR-125a-5p and downregulation of miR-518a-5p increase cell viability [65]. miR-107 is associated with imatinib resistance [64]. miR-218 increases the sensitivity of GIST cells to imatinib due to the inhibition of PI3K/AKT pathway [66]. Again, miR-504, miR-100, miR214, miR-210, miR-222 and miR-132 are differentially expressed depending on the tumor location, mutation status and tumor risk of GISTs [67]. This evidence supports the hypothesis that miRNAs can act as functional oncogenes or tumor suppressors involved in the development and progression of GIST.

4.4. Pharmacogenetics modulating treatment response

In addition to somatic DNA's primary function of determining the clinical response to TKIs, various genetic variations that impact the way TKIs are processed and their effects have been recognized as potential contributors. Indeed, there is considerable variability in how individuals respond to targeted therapies, and the status of mutations seems to play a crucial role in predicting the initial response [68]. However, tumor genotype can only partially account for this variability, and it's important to take into consideration the patient's germline DNA. Germline DNA influences drug pharmacokinetics, which indirectly impacts drug efficacy and toxicity. Therefore, variations in DNA, such as polymorphisms, may influence the overall clinical response to the drug.

Over the past decade, a bunch of studies have investigated the role of SNPs on imatinib and sunitinib response. Several polymorphisms in transporter and metabolizing genes influencing the pharmacokinetics of imatinib have been identified, either associated with efficacy [69–72] or toxicity [73–75], as well as for sunitinib [76–78]. However, the current data is not sufficiently definitive to be applied in clinical practice or to forecast the effectiveness or potential harm in the adjuvant and neoadjuvant context, mainly due to the small size of population cohorts involved in these studies.

5. Treatment

5.1. Radiotherapy

While surgery remains the primary treatment for GIST, adjuvant imatinib is often recommended for high-risk tumors. Radiation therapy can be a valuable option for patients who i) cannot tolerate or are resistant to TKI drugs [79,80], ii) have an unresectable tumor, iii) have residual disease after surgery. Radiation therapy has shown promise in improving symptoms for some GIST patients with advanced or metastatic disease. Further research is needed to fully understand the efficacy and safety of radiation therapy in GIST patients [81].

5.2. Localized disease

Surgery is the primary treatment for localized GISTs and is often performed laparoscopically (Fig. 4) [82,83]. The primary goal of GIST surgery is to achieve complete resection (R0) while minimizing organ damage and preventing tumor rupture. Tyrosine Kinase Inhibitor (TKIs) targets several proteins involved in GISTs growth and survival, including ABL, BCR-ABL, KIT, PDGFRA, PDGFRB, and CSF1R (Fig. 1). Patients with advanced GIST who receive imatinib have a significant survival benefit, with 9-year survival rates ranging from 35 % to 49 % [84]. The specific KIT or PDGFRA mutation status is a key predictor of response to imatinib. Exon 11 mutations (Fig. 1), which occur in the KIT juxtamembrane domain, are the most common mutations in GISTs and are generally associated with better response to imatinib, with longer progression-free survival (PFS) and overall survival (OS). GISTs with KIT exon 9 mutation also benefit from imatinib but are less sensitive to the standard dose of 400 mg/die and benefit from the increased dose of imatinib 800 mg/die [85]. PDGFRA mutations, primarily affecting exon 18 in the tyrosine kinase domain, are common in gastric GIST. While higher doses of imatinib may be associated with more side effects, 400 mg/day is equally effective in terms of response rates and

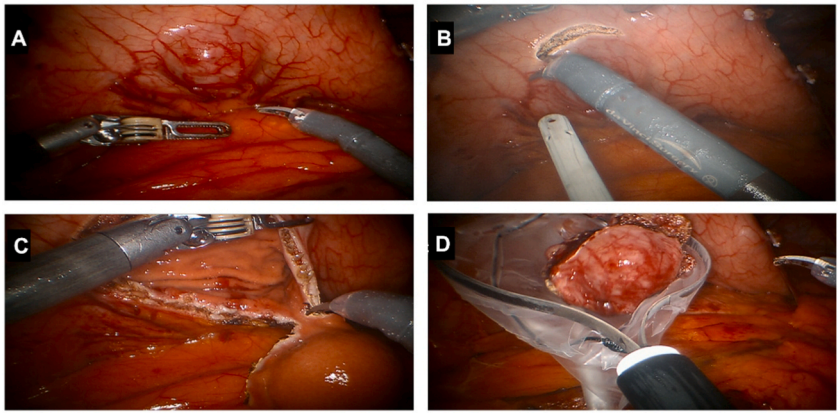


Fig. 4. Representative images of GIST tumor appearance. (A) Surgical intervention initial vision, (B) Margin widening; (C) Termination of excision; (D) Retrieval bag.

overall survival [86,87]. The benefits of neoadjuvant imatinib include cytoreduction to facilitate R0 resection, the organ preservation, a less invasive surgical approach, and attendant reductions in the risk of intraoperative bleeding or tumor rupture [88].

5.3. Advanced and metastatic disease

GISTs typically metastasize to the liver and peritoneum [87]. The development of second- and third-line drugs like Sunitinib and Regorafenib has significantly extended the survival of patients with advanced or metastatic GIST (Table 3) [88]. Sunitinib is a multitargeted TKI inhibitor of alpha-type and beta-type PDGFR and VEGFR receptors [89]. The recommended dose is 50 mg orally once a day over 4 weeks followed by a 2-week rest period [88,89]. Regorafenib is an orally active multikinase inhibitor with activity against KIT. It is recently approved by FDA and EMA in the treatment of patients with unresectable/metastatic GIST or intolerant to imatinib and sunitinib. For the first 21 days of each 28-day cycle, the recommended dose is 160 mg taken orally once daily. Treatment cycles with Regorafenib typically continue until the disease progresses or intolerable side effects develop [80]. We herein provide an overview of contemporary approaches to the discovery of small molecule cancer drugs, highlighting mutation site and chemical structure (Table 4).

6. Future perspective in nanotechnology-based biomaterials

6.1. Nanotechnology and drug delivery system

The restrictions of current diagnostic techniques, as well as the low stability, availability, and/or specificity of pharmacological treatment, represent the main limitations in the management of GISTs. In recent years, nanotechnology has emerged as a promising field with significant potential in early diagnosis, comprehensive study, and targeted treatment. Conventional cancer chemotherapy is often limited by factors such as short circulation time, low drug concentrations in the target area, poor water solubility, and harmful side effects caused by widespread distribution. These limitations can reduce treatment effectiveness and negatively impact patient well-being. Therefore, drug systems operating at nanoscales have emerged as an improved pharmacokinetic approach to overcoming the deficiencies of current combination therapies. Nanoparticles (NP) (Fig. 5) are colloidal carriers varying between 1 and 1000 nm in size with natural or synthetic origins. Nanoparticles (NPs) offer several advantages for cancer drug delivery, including high specificity, increased efficiency, excellent stability, and reduced toxicity. A wide range of nanocarriers are available, in particular metal-based NPs, polymer-based NPs, and liposomes [101–103]. In this review, we also highlighted recent advancements in smart nanoparticles, including polymeric nanoparticles, micelles, liposomes, protein nanoparticles, cell membrane nanoparticles, gold nanoparticles, iron oxide nanoparticles, carbon nanotubes, and others. These smart nanoparticles possess the ability to respond to various external and internal stimuli, such as enzymes, pH, temperature, optics, and magnetism, making them intelligent systems. Focused examples of nanostructured materials for treating gastrointestinal disorders are presented below.

Enzymes are widely present in the tissues and organs to maintain the normal operation of the human body. The tumor microenvironment exhibits aberrant expression of enzymes such as phospholipases and oxidoreductases because tumor cells grow more quickly than other normal organs and require more enzymes for functional support. Phospholipase can hydrolyze phospholipids into fatty acids and other lipophilic substances. Phospholipase is overexpressed in inflammation and peripheral sites of tumor invasion. Secretory phospholipase A2 (sPLA2) is associated with the pathology of colorectal, gastric, oesophageal and prostate cancers, which provide the potential for phospholipase to be designed as a stimulator in releasing drugs. In addition, hyaluronidase, γ-Glutamyltranspeptidase, prostate-specific antigen, Trysin, β-galactosidase, etc. are also used in enzyme-stimulated response smart nano-delivery systems. Poly (lactic-co-glycolic acid) micro/nanoparticles (PLGA M/NPs) have good biocompatibility, biodegradability and unique physical and chemical properties, making them one of the most popular and effective drug delivery polymers. PLGA is used as drug delivery systems due to their excellent biocompatibility and biodegradability, but they cannot easily adhere to certain negatively charged mucous membranes because of their inherent negative charge. The functionalization of PLGA with cyclodextrin (Cyclodextrin-PLGA nanoparticles) can enhance their uptake by gastrointestinal cancer cells [104]. Different nanocarriers have different structures and properties, and suitable nanocarriers can be selected in accordance with the nature of the drug delivered. For example, micelles are suitable for the delivery of water-insoluble and amphiphilic drugs increasing the cellular uptake of a variety of drugs [105]. The polymeric nanoparticles represent an important revolution in biomedical applications. Polymeric nanoparticles have several advantages over non-mixed drugs, in terms of cycle time, stability, structural decomposition, encapsulation rate, premature release, and nonspecific release kinetics. Other advances involve the capability of combining materials with different chemical compositions such as organic-organic and organic-inorganic materials to achieve synergistic properties [106]. Polymeric nanoparticles (proteins, and liposomes) with a disulfide linker [107], are specifically tested in gastrointestinal tumors to improve drug therapeutic efficacy. To address disease recurrence and resistance, a recent study published in Pharmaceuticals explored a novel drug delivery system based on esterase-responsive polyglycerol nanogels (NGs) [108]. A novel drug delivery system was developed using nanoprecipitation mediated by inverse electron-demand Diels-Alder cyclizations. This method created multi-drug-loaded nanogels with exceptional stability in biological environments [108]. Cell viability and live cell imaging studies revealed that the loaded NGs are capable of intracellular drug release by showing similar IC50 values to those of the free drugs. Furthermore, multi-drug-loaded NGs were capable of overcoming cell resistance, demonstrating the utility of this carrier system. The most promising application for Nps is the transport of imatinib mesylate, which is poorly soluble in water and has a very low bioavailability. Imatinib mesylate was incorporated in Nps with a chitosan surface and polyglutamic acid core. Compared to standard imatinib, this new formulation offers several advantages, including lower effective dosage, improved bioavailability, and consistent pharmacokinetics [109].

Table 3
Common GIST mutation types, location, and treatment.

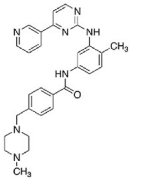
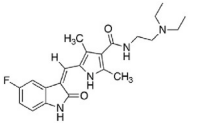
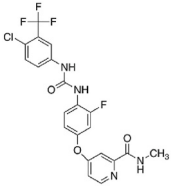
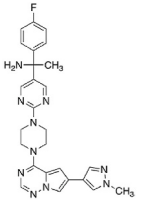
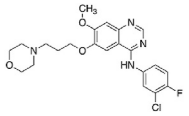
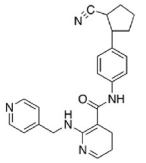
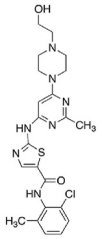
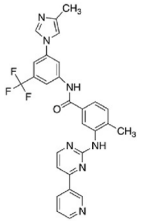
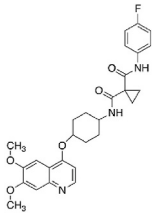
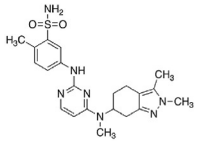
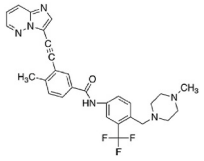
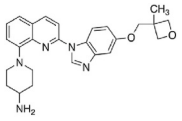
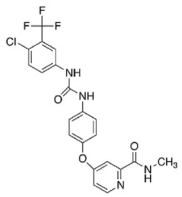
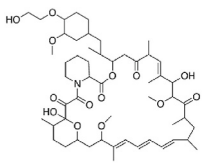
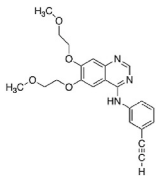
Genes mutation	*Approximate frequency (%)*	Location	Common mutation	Prognostic factors	Treatment	Chemical structure
c-KIT *exon 11*	65	All sites	557-558 codon	Higher response rate	Imatinib	
c-KIT *exon 9*	10	Small intestine	2A502_Y503 codon repetition	Unfavorable prognosis	Imatinib high dose required	–
c-KIT *exon 13, 17*	1	Small intestine	Lys642Glu, Asn822Lys	Larger and aggressive	Sunitinib	
PDGFRa *exon 18*	6	Stomach	p.D842V	Low mitotic count and favorable prognosis	Regorafenib	
PDGFRa *exon 14*	1.5	Stomach	p.N659K	Better prognosis	Avapritinib	
PDGFRa *exon 12*	>1	5.8 % gastric 1.9%intestinal	V561D missense mutation	Difficult to judge the prognosis	Imatinib	–
Other mutations	12	–	SDH-deficient NF1 BRAF KRAS	Difficult to judge the prognosis	Sunitinib, regorafenib or other TKIs	–

Table 4
Investigated and currently under investigation drugs.

Treatment	Mutation	Chemical structure	References
gefitinib	imatinib-resistant mutations		[90]
apatinib	KIT mutation in exon 11		[91]
dasatinib	PDG- FRA D842V mutation		[92]
nilotinib	KIT exon 17 mutations		[93]
cabozantinib	KIT exon 9, exon 13, and exon 14		[94]
pazopanib	KIT mutations		[95]
ponatinib	KIT exon 17 D816-mutant kinases		[96]
crenolanib	PDGFRA D842V mutation		[97]

(*continued on next page*)

Table 4 (*continued*)

Treatment	Mutation	Chemical structure	References
sorafenib	imatinib-resistant mutations		[98]
everolimus	imatinib-resistant mutations		[99]
erlotinib	imatinib-resistant mutations		[100]

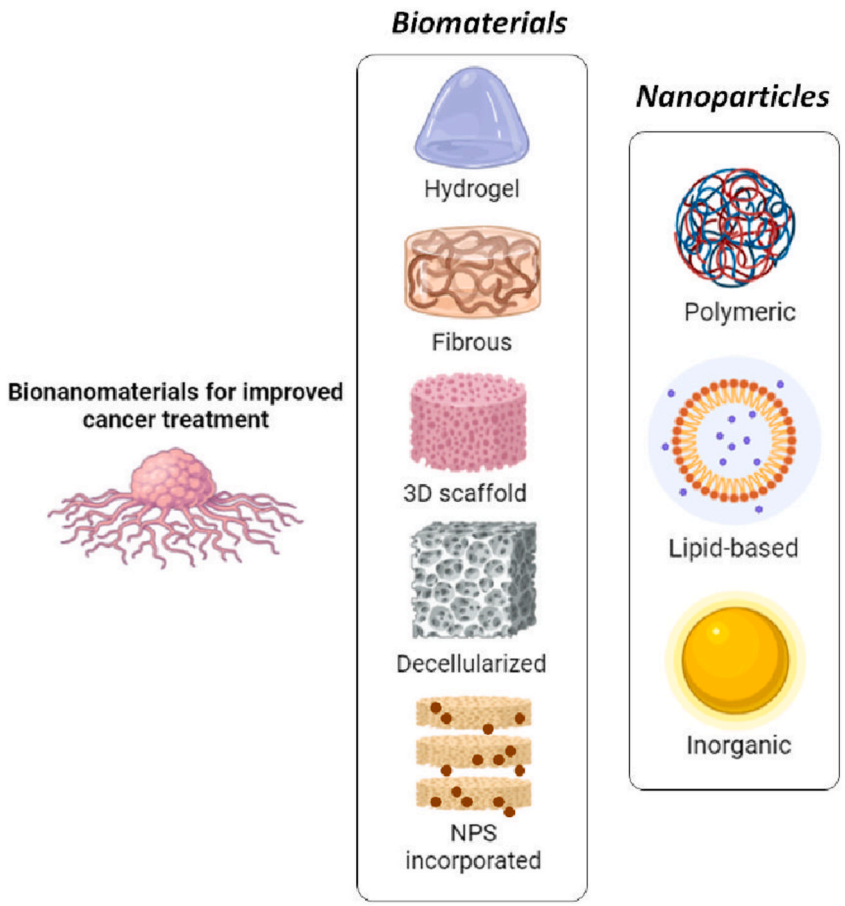


Fig. 5. Representative images of the main classes of biomaterials used in 3D scaffold production and drug delivery systems.

The positive charge on the chitosan surface also enhances the permeability for delivery of the bioactive agent [110–112]. The pH-responsive nanoparticles against the tumor extracellular and intracellular stress are the most investigated to date. Almost all solid tumors are prone to speeding up the rate of glycolysis by generating a bulking amount of lactic acid to provide adequate energy for tumor cells (Warburg effect) [106]. The acidic microenvironment of gastric tumor is the origin of the design of pH-responsive smart nanoparticles. Smart biodegradable Np/pH dependent [113], Nps containing PCT and albumin, and perfosine combined with a drug-loaded Np are some other examples of novel therapeutic strategies for targeting c-KIT mutations. pH-responsive NPs can optimize drug delivery and potency by actively responding to environmental cues. A promising area of nanotechnology in GIST research involves the use of carbon nanotubes loaded with nucleic acids (UDP-glucuronosyltransferases or p53) or drugs such as sorafenib tosylate [114]. In the form of hollow spheres, ellipsoids, tubes, and many other shapes, carbon nanotubes (CNTs) are a type of fullerene, a class of carbon allotropes [106]. Consequently, by overcoming limitations associated with conventional drug delivery, nanotechnology-based therapies have the potential to enhance treatment efficacy and improve patient outcomes.

6.2. Tumor microenvironment in a 3D scaffold model

The tumor microenvironment (TME) profoundly influences cancer cell behavior, regulating tumor progression and therapeutic response. To recapitulate the complex TME *in vitro*, three-dimensional (3D) culture systems have emerged as powerful tools. By mimicking the structural and biochemical regions of the extracellular matrix (ECM), these systems enable a more physiologically relevant representation of tumor growth and metastasis. Polymeric scaffolds have become the cornerstone of 3D cancer models, providing the necessary structural support for cell proliferation and interaction. The physio-chemical and mechanical environments of 3D culture (Fig. 5) allow cancer cells to expand in a heterogeneous manner, adopting different phenotypes, gene and protein profiles, and developing metastatic potential and drug resistance similar to human tumors. This paragraph will focus on the recent advancement of numerous 3D-based scaffold models for cancer tissue engineering (Table 5), which will increase the predictive ability of preclinical studies and significantly improve clinical translation.

The hybrid fibrous scaffold models are employed in many cancer types. Pal et al. developed a 3D hybrid scaffold model composed of Poly Lactic-co-Glycolic Acid (PLGA) fibres and GelMA hydrogel, which recapitulates the *in vivo* ECM better than GelMA or PLGA scaffold alone [115]. Poly (3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) and PHBV/CP (collagen peptide) are biocompatible nanofiber scaffolds produced by the electrospinning method. These biomimetic polymers are used for the chemosensitivity assay of anticancer drugs due to their strong influence on cell growth and resistance to anticancer drugs [116]. Bioprinted cancer models are an alternative to nanofiber scaffolds and offer a wide range of uses, including drug screening, development, and delivery, cancer modeling, and regenerative medicine. Three-Dimensional Microfilament Printing of a Decellularized Extracellular Matrix (dECM) Bioink Derived from Porcine Decellularized Gastric Tissues (g-dECM) could be an example. The presence of cellulose nanoparticles in g-dECM [117] confers stability, compactness, and system order, mimicking the biological and structural conditions observed *in vivo*. Anyway, some limitations such as sample manipulations, repopulation rate, diffusion of oxygen and nutrients should be considered [118]. The synthesis of a patient-derived hydrogel offers a partial solution. Hydrogels are highly hydrated polymers which maintain structural integrity through physical and chemical crosslinks among polymer chains. The typical dECM-mimetic hydrogel consists in collagen-based self-assembly partially regulated by glycosaminoglycans, proteoglycans, and ECM proteins. It was proposed to develop *in vitro* tissue models with physiologically realistic geometries at microscale resolutions to approximate the actual density and size of human intestinal villi [118]. The coupling of hydrogels with microspheres or nanoparticles functionalized by ECM components and small molecules is a subsequent advancement in the development of high-performance scaffolds for tissue engineering [119,120]. In conclusion, two-dimensional (2D) cell cultures have been traditionally applied in cancer research and are still a dominant culture method in many biological studies. Cell-based assays are essential in the drug discovery and validation process, and 2D cell culture

Table 5
Advantages and disadvantages of different scaffolds in tissue engineering.

Type of scaffolds	Advantages	Disadvantages
Hydrogels	• Tissue-like responsiveness • Generally biocompatible	Minimal mechanical resistance
3D Bioprinted scaffolds	• High-reproducibility of biomimetic microenvironments • Homogeneous distribution of cells • High mechanical resistance	Minimal diffusion of nutritional factors
Decellularized scaffolds	• Provides ECM environment • High bioactivity • Promotion of cell-material interactions	• Difficulties in decellularization protocol; • Minimal number of adhesiveness of cells
Fibrous scaffolds	High surface-area-to-volume favouring cell proliferation, migration, adhesion and differentiation of cells	• Low structural stability; • Unregulated scaffold morphology; • Small pore-size
Microsphere scaffolds	• Releasing of encapsulated bioactive molecules • Long-time maintenance cell-culture • Excellent mechanical properties	Expensive
Nanoparticle incorporated scaffolds	• High penetration • Functionalized surface	Particle aggregation

offers a platform for investigating cell physiology and disease outside of the organism. Due to the complexity of the cellular micro-environment, 2D cell cultures cannot perfectly replicate or reproduce the *in vivo* conditions. 2D cultures are characterized by unnatural growth kinetics, altered proliferation, behavior, and reaction to toxicants compared to *in vivo* environments. Hence, there is an important necessity to develop conditions that mimic human physiology. The most common type of three-dimensional (3D) tissue culture employed are 3D scaffold models. A biocompatible and biodegradable 3D scaffold system incorporating the biological and chemical characteristics of tumor-specific ECM would maximize mimicry and the power of *in vitro* studies. Although 3D culture is typically superior to 2D culture, biological indicators from cells grown in 3D systems can be confusing in respect to the scaffolding materials, synthesis and model designs. Different scaffolding materials, such as collagen, fibronectin etc., activate the functionally diverse cell receptors, making the system understandable. Therefore, selecting appropriate bio-polymers to address specific questions remains a challenge for the scaffold-engineering field. Despite these limitations, 3D models provide a more realistic starting point for understanding the cellular and molecular pathways involved in cancer cell/biomatrix interactions.

7. Conclusion and remarks

GISTs are rare tumors that account for a small percentage of gastrointestinal neoplasms, usually identified by CT scan associated with abdominal ultrasound, MRI, and PET. The pathological profile consists of spindle cells, epithelioid cells or mixed cell types that commonly stain positive for c-Kit and DOG-1. To assess the risk of malignancy and recurrence, specific indicators are employed, including tumor size, mitotic rate and location. The first line of GISTs treatment is imatinib, also used as adjuvant therapy post laparoscopic surgical resection. Metastasis, in advanced GIST, occurs in the liver, mesentery and omentum, and are treated as high risk GISTs. In the last year, FDA approved sunitinib, and regorafenib as second-third treatment line. Sunitinib is exploited for c-Kit exon 9, 13, or 14 mutations, while regorafenib is used in highly refractory tumors.

Currently, the survival of GIST patients has considerably increased compared to historical data. Adjuvant and advanced GIST settings benefit from diverse authorized treatment: Avapritinib, Ayvakit (Avapritinib), Gleevec (Imatinib Mesylate), Imatinib Mesylate, Qinlock (Ripretinib), Regorafenib, Ripretinib, Stivarga (Regorafenib), Sunitinib Malate, Sutent (Sunitinib Malate) and other which are undergoing experimental phase. Anyway, the complexity of GISTs necessitates more extensive exploration of new treatment approaches. Nanotechnology offers a promising avenue for addressing the limitations of traditional cancer treatments. By encapsulating drugs within nanoparticles, researchers can enhance drug delivery, specifically target tumors, and reduce side effects. Various nanoparticle types, including those derived from metals, polymers, and lipids, are being investigated for their potential in treating GISTs. Additionally, nanotechnology is contributing to improving diagnostic tools and a deeper understanding of tumor biology through three-dimensional cell culture models. Nanofibrous scaffolds are artificial extracellular matrices which provide a natural environment for tissue generation. In comparison to other forms of scaffolds, the nanofibrous scaffolds promote cell adhesion, proliferation and differentiation due to the high surface and volume ratio. Scaffolds for tissue engineering have been synthesized by various techniques, including electrospinning, nanoprecipitation and fiber swelling. These models offer advantages for screening, development, and delivery of drugs. Although rapid prototyping techniques may have several advantages, some limitations and challenges still remain. Challenges in manipulation, cell engraftment, and diffusion of nutrients may need to be addressed. While significant progress has been made in GIST management, further research is essential to develop more effective and personalized treatments. By combining advancements in nanotechnology with a comprehensive understanding of GIST biology, the medical community can work towards improving patient outcomes and ultimately achieving a cure.

CRediT authorship contribution statement

Sofia Gabellone: Writing – original draft, Conceptualization. **Silvia Vanni:** Writing – review & editing, Conceptualization. **Valentina Fausti:** Writing – review & editing. **Giacomo Miserocchi:** Writing – review & editing. **Chiara Liverani:** Writing – review & editing. **Chiara Spadazzi:** Writing – review & editing. **Claudia Cocchi:** Writing – review & editing. **Chiara Calabrese:** Writing – review & editing. **Davide Cavaliere:** Writing – review & editing. **Carlo Alberto Pacilio:** Writing – review & editing. **Giorgio Ercolani:** Writing – review & editing. **Federica Pieri:** Writing – review & editing. **Lorena Gurrieri:** Writing – review & editing. **Nada Riva:** Writing – review & editing. **Robin Jones:** Writing – review & editing. **Alessandro De Vita:** Writing – original draft, Conceptualization.

Ethical approval and consent to participate

Not applicable.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

This work was supported by an Italian Ministry of Health grant for the project GR-2021-12372877.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Alessandro De Vita reports financial support was provided by Italian ministry of health. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] E. Merry, K. Thway, R.L. Jones, P.H. Huang, Predictive and prognostic transcriptomic biomarkers in soft tissue sarcomas, npj Precis. Oncol. 5 (1) (Mar. 2021) 17, https://doi.org/10.1038/s41698-021-00157-4, 10.1038/s41698-021-00157-4.

[2] J.Y. Blay, Y.K. Kang, T. Nishida, von M. Mehren, Gastrointestinal stromal tumours, Nat. Rev. Dis. Prim. 7 (1) (Mar. 2021) 22, https://doi.org/10.1038/s41572-021-00254-5.

[3] A. Diamantis, et al., Gastrointestinal stromal tumor (GIST) and synchronous intra-abdominal liposarcoma: a report of two rare cases and literature review, Int. J. Surg. Oncol. 2021 (Sep. 2021) 2626635, https://doi.org/10.1155/2021/2626635.

[4] P. Radu, et al., Interstitial cells of cajal-origin, distribution and relationship with gastrointestinal tumors, Medicina 59 (1) (Dec. 2022) 63, https://doi.org/10.3390/medicina59010063.

[5] S.J. Xu, S.Y. Zhang, L.Y. Dong, G.S. Lin, Y.J. Zhou, Dynamic survival analysis of gastrointestinal stromal tumors (GISTs): a 10-year follow-up based on conditional survival, BMC Cancer 21 (1) (Nov. 2021) 170, https://doi.org/10.1186/s12885-021-08828-y.

[6] N.S. Ijzerman, et al., Gastrointestinal stromal tumours (GIST) in young adult (18-40 Years) patients: a report from the Dutch GIST registry, Cancers (Basel) 12 (3) (Mar. 2020) 730, https://doi.org/10.3390/cancers12030730.

[7] F. Cuccaro, et al., Population-based incidence of gastrointestinal stromal tumors in Puglia, Tumori 107 (1) (Feb. 2021) 39–45, https://doi.org/10.1177/0300891620931944.

[8] F. Catalano, et al., Molecular tailored therapeutic options for advanced gastrointestinal stromal tumors (GISTs): current practice and future perspectives, Cancers 15 (7) (Mar. 2023) 2074, https://doi.org/10.3390/cancers15072074.

[9] C.R. Antonescu, et al., Association of KIT exon 9 mutations with nongastric primary site and aggressive behavior: KIT mutation analysis and clinical correlates of 120 gastrointestinal stromal tumors, Clin. Cancer Res. 9 (9) (Ago. 2003) 3329–3337.

[10] H. Zhang, Q. Liu, Prognostic indicators for gastrointestinal stromal tumors: a review, Transl. Oncol. 13 (10) (Oct. 2020) 100812, https://doi.org/10.1016/j.tranon.2020.100812.

[11] A.D. Tan, et al., Tyrosine kinase inhibitors significantly improved survival outcomes in patients with metastatic gastrointestinal stromal tumour: a multi-institutional cohort study, Curr. Oncol. 27 (3) (Jun. 2020) e276–e282, https://doi.org/10.3747/co.27.5869.

[12] G.D. Demetri, et al., Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial, Lancet 381 (9863) (Jan. 2013) 295–302, https://doi.org/10.1016/S0140-6736(12)61857-1.

[13] M. Liang, L.D. Li, L. Li, S. Li, Nanotechnology in diagnosis and therapy of gastrointestinal cancer, World J. Clin. Cases 10 (16) (Jun 2022) 5146–5155, https://doi.org/10.12998/wjcc.v10.i16.5146.

[14] M. Miettinen, J. Lasota, Gastrointestinal stromal tumors–definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis, Virchows Arch. 438 (1) (Jan. 2001) 1–12, https://doi.org/10.1007/s004280000338.

[15] G. Gheorghe, et al., Gastrointestinal stromal tumors-A mini review, J. Personalized Med. 11 (8) (Jul. 2021) 694, https://doi.org/10.3390/jpm11080694.

[16] J.S. Kim, et al., Computed tomography features and predictive findings of ruptured gastrointestinal stromal tumours, Eur. Radiol. 27 (6) (Jun. 2017) 2583–2590, https://doi.org/10.1007/s00330-016-4515-z.

[17] J. Martín, et al., Deletions affecting codons 557-558 of the c-KIT gene indicate a poor prognosis in patients with completely resected gastrointestinal stromal tumors: a study by the Spanish Group for Sarcoma Research (GEIS), J. Clin. Oncol. 23 (25) (Sept. 2005) 6190–6198, https://doi.org/10.1200/JCO.2005.19.554.

[18] B.K. Goh, et al., Outcome after laparoscopic versus open wedge resection for suspected gastric gastrointestinal stromal tumors: a matched-pair case-control study, Eur. J. Surg. Oncol. 41 (7) (Jul. 2015) 905–910, https://doi.org/10.1016/j.ejso.2015.04.001.

[19] S.B. Edge, American Joint Committee on Cancer; American Cancer Society, AJCC Cancer Staging Handbook: from the AJCC Cancer Staging Manual, seventh ed., 2010. New York.

[20] C. Jumniensuk, M. Charoenpitakchai, Gastrointestinal stromal tumor: clinicopathological characteristics and pathologic prognostic analysis, World J. Surg. Oncol. 16 (1) (Dec. 2018) 231, https://doi.org/10.1186/s12957-018-1532-1.

[21] B.P. Rubin, Gastrointestinal stromal tumours: an update, Histopathology 48 (1) (Jan. 2006) 83–96, https://doi.org/10.1111/j.1365-2559.2005.02291.

[22] I.M. Schaefer, R.P. DeMatteo, C. Serrano, The GIST of advances in treatment of advanced gastrointestinal stromal tumor, Am. Soc. Clin. Oncol. Educ. Book 42 (Apr) (2022) 1–15, https://doi.org/10.1200/EDBK_351231.

[23] I. Brčić, A. Argyropoulos, B. Liegl-Atzwanger, Update on molecular genetics of gastrointestinal stromal tumors, Diagnostics 11 (2) (Jan. 2021) 194, https://doi.org/10.3390/diagnostics11020194.

[24] S. Pathania, O.T. Pentikäinen, P.K. Singh, A holistic view on c-Kit in cancer: structure, signaling, pathophysiology and its inhibitors, Biochim. Biophys. Acta Rev. Canc 1876 (2) (Dec. 2021) 188631, https://doi.org/10.3390/10.1016/j.bbcan.2021.188631.

[25] S. Ali, S. Ali, Role of c-kit/SCF in cause and treatment of gastrointestinal stromal tumors (GIST), Gene 401 (1–2) (Oct. 2007) 38–45, https://doi.org/10.1016/j.gene.2007.06.017.

[26] L. Rönnstrand, Signal transduction via the stem cell factor receptor/c-Kit, Cell. Mol. Life Sci. 61 (19–20) (Oct. 2004) 2535–2548, https://doi.org/10.1007/s00018-004-4189-6.

[27] P.J. Oppelt, A.C. Hirbe, B.A. Van Tine, Gastrointestinal stromal tumors (GISTs): point mutations matter in management, a review, J. Gastrointest. Oncol. 8 (3) (Jun. 2017) 466–473, https://doi.org/10.21037/jgo.2016.09.15.

[28] A.E. Bannon, L.R. Klug, C.L. Corless, M.C. Heinrich, Using molecular diagnostic testing to personalize the treatment of patients with gastrointestinal stromal tumors, Expert Rev. Mol. Diagn. 17 (5) (May 2017) 445–457, https://doi.org/10.1080/14737159.2017.1308826.

[29] E. Shi, et al., FGFR1 and NTRK3 actionable alterations in “Wild-Type” gastrointestinal stromal tumors, J. Transl. Med. 14 (1) (Dec. 2016) 339, https://doi.org/10.1186/s12967-016-1075-6.

[30] X. Xiao, W. Yuan, C. Wang, H. Song, A systematic review and network meta-analysis of the efficacy and safety of third-line and over third-line therapy after imatinib and TKI resistance in advanced gastrointestinal stromal tumor, Front. Pharmacol. 13 (Nov) (2022) 978885, https://doi.org/10.3389/fphar.2022.978885.

[31] W. El-Rifai, M. Sarlomo-Rikala, L.C. Andersson, S. Knuutila, M. Miettinen, DNA sequence copy number changes in gastrointestinal stromal tumors: tumor progression and prognostic significance, Cancer Res. 60 (14) (Jul. 2000) 3899–3903.

[32] W. Zhou, X. Zeng, T. Liu, Aberrations of chromosome 13q in gastrointestinal stromal tumors: analysis of 91 cases by fluorescence in situ hybridization (FISH), Diagn. Mol. Pathol. 18 (2) (Jun 2009) 72–80, https://doi.org/10.1097/PDM.0b013e318181fa1f.

[33] A. Sen, R. Gangavatiker, EXON 11, C KIT mutation in a ’CD 117’ & ’DOG 1’ negative colonic gastrointestinal tumor, Med. J. Armed Forces India 70 (2) (Apr. 2014) 186–188, https://doi.org/10.1016/j.mjafi.2013.07.011.

[34] J. Martin-Broto, et al., Gastrointestinal stromal tumors (GISTs): SEAP-SEOM consensus on pathologic and molecular diagnosis, Clin. Transl. Oncol. 19 (5) (May 2017) 536–545, https://doi.org/10.1007/s12094-016-1581-2.
[35] R.B. West, et al., The novel marker, DOG1, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of KIT or PDGFRA mutation status, Am. J. Pathol. 165 (1) (Jul. 2004) 107–113, https://doi.org/10.1016/S0002-9440(10)63279-8.
[36] W.Y. Zhao, et al., Prognostic value of Ki67 index in gastrointestinal stromal tumors, Int. J. Clin. Exp. Pathol. 7 (5) (Apr. 2014) 2298–2304.
[37] P. Blay, et al., Protein kinase C theta is highly expressed in gastrointestinal stromal tumors but not in other mesenchymal neoplasias, Clin. Cancer Res. 10 (12 Pt 1) (Jun. 2004) 4089–4095, https://doi.org/10.1158/1078-0432.CCR-04-0630.
[38] M. Miettinen, Z.F. Wang, J. Lasota, DOG1 antibody in the differential diag- nosis of gastrointestinal stromal tumors: a study of 1840 cases, Am. J. Surg. Pathol. 33 (9) (Sep. 2009) 1401–1408, https://doi.org/10.1097/PAS.0b013e3181a90e1a.
[39] G. Ceccarelli, et al., Minimally invasive approach to gastric GISTs: analysis of a multicenter robotic and laparoscopic experience with literature review, Cancers (Basel) 13 (17) (Aug. 2021) 4351, https://doi.org/10.3390/cancers13174351.
[40] F. Vernuccio, et al., Imaging of gastrointestinal stromal tumors: from diagnosis to evaluation of therapeutic response, Anticancer Res. 36 (6) (Jun. 2016), 2639-2348.
[41] G.Y. Pih, D.H. Kim, Endoscopic ultrasound-guided fine needle aspiration and biopsy in gastrointestinal subepithelial tumors, Clin. Endosc. 52 (4) (Jul. 2019) 314–320, https://doi.org/10.5946/ce.2019.100.
[42] D. Gómez-Peregrina, et al., Liquid biopsy in gastrointestinal stromal tumors: ready for prime time? Curr. Treat. Options Oncol. 22 (4) (Feb. 2021) 32, https://doi.org/10.1007/s11864-021-00832-5.
[43] G. Calderillo-Ruíz, et al., Genomic profiling in GIST: implications in clinical outcome and future challenges, Neoplasia 48 (Feb) (2024) 100959, https://doi.org/10.1016/j.neo.2023.100959.
[44] Z. Chen, R.M. Lin, Y.K. Bai, Y. Zhang, Establishment and verification of prognostic nomograms for patients with gastrointestinal stromal tumors: a SEER-based study, BioMed Res. Int. (Mar. 2019) 8293261, https://doi.org/10.1155/2019/8293261, 2019.
[45] X. Zhi, X. Zhou, W. Wang, Z. Xu, Practical role of mutation analysis for imatinib treatment in patients with advanced gastrointestinal stromal tumors: a meta-analysis, PLoS One 8 (11) (Nov. 2013) e79275, https://doi.org/10.1371/journal.pone.0079275.
[46] A. Wozniak, et al., Tumor genotype is an independent prognostic factor in primary gastrointestinal stromal tumors of gastric origin: a European multicenter analysis based on ConticaGIST, Clin. Cancer Res. 20 (23) (Dic. 2014) 6105–6116, https://doi.org/10.1158/1078-0432.CCR-14-1677.
[47] J. Lasota, et al., Mutations in exons 9 and 13 of KIT gene are rare events in gastrointestinal stromal tumors. A study of 200 cases, Am. J. Pathol. 157 (4) (Oct. 2000) 1091–1095, https://doi.org/10.1016/S0002-9440(10)64623-8.
[48] B. Pasini, et al., Clinical and molecular genetics of patients with the Carney-Stratakis syndrome and germline mutations of the genes coding for the succinate dehydrogenase subunits SDHB, SDHC, and SDHD, Eur. J. Hum. Genet. 16 (1) (Jan. 2008) 79–88, https://doi.org/10.1038/sj.ejhg.5201904.
[49] Y.Y. Shen, et al., Exon 11 homozygous mutations and intron 10/exon 11 junction deletions in the KIT gene are associated with poor prognosis of patients with gastrointestinal stromal tumors, Cancer Med. 9 (18) (Sep. 2020) 6485–6496, https://doi.org/10.1002/cam4.3212.
[50] Z.M. Bamboat, R.P. Dematteo, Updates on the management of gastrointestinal stromal tumors, Surg. Oncol. Clin. N. Am. 21 (2) (Apr. 2012) 301–316, https://doi.org/10.1016/j.soc.2011.12.004.
[51] J.S. Gold, et al., Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis, Lancet Oncol. 10 (11) (Nov. 2009) 1045–1052, https://doi.org/10.1016/S1470-2045(09)70242-6.
[52] B.K. Goh, et al., Outcome after laparoscopic versus open wedge resection for suspected gastric gastrointestinal stromal tumors: a matched-pair case-control study, Eur. J. Surg. Oncol. 41 (7) (Jul. 2015) 905–910, https://doi.org/10.1016/j.ejso.2015.04.001.
[53] M. von Mehren, et al., Soft tissue sarcoma, version 2.2012: featured updates to the NCCN guidelines, J. Natl. Compr. Cancer Netw. 10 (8) (Aug. 2012) 951–960, https://doi.org/10.6004/jnccn.2012.0099.
[54] U. Gyvyte, et al., MiRNA profiling of gastrointestinal stromal tumors by next-generation sequencing, Oncotarget 8 (23) (Jun. 2017) 37225–37238, https://doi.org/10.18632/oncotarget.16664.
[55] R. Steponaitiene, et al., Epigenetic silencing of miR-137 is a frequent event in gastric carcinogenesis, Mol. Carcinog. 55 (4) (Apr. 2016) 376–386, https://doi.org/10.1002/mc.22287.
[56] F. Haller, et al., Localization- and mutation-dependent microRNA (miRNA) expression signatures in gastrointestinal stromal tumours (GISTs), with a cluster of co-expressed miRNAs located at 14q32.31, J. Pathol. 220 (1) (Jan 2010) 71–86, https://doi.org/10.1002/path.2610.
[57] T. Niinuma, et al., Upregulation of miR-196a and HOTAIR drive malignant character in gastrointestinal stromal tumors, Cancer Res. 72 (5) (Mar. 2012) 1126–1136, https://doi.org/10.1158/0008-5472.CAN-11-1803.
[58] P. Akçakaya, et al., microRNA expression signatures of gastrointestinal stromal tumours: associations with imatinib resistance and patient outcome, Br. J. Cancer 111 (11) (Nov.2014) 2091–2102, https://doi.org/10.1038/bjc.2014.548.
[59] H. Tong, et al., Expression profile of microRNAs in gastrointestinal stromal tumors revealed by high throughput quantitative RT-PCR microarray, World J. Gastroenterol. 21 (19) (May 2015) 5843–5855, https://doi.org/10.3748/wjg.v21.i19.5843.
[60] R. Fan, et al., microRNA-218 increase the sensitivity of gastrointestinal stromal tumor to imatinib through PI3K/AKT pathway, Clin. Exp. Med. 15 (2) (May 2015) 137–144, https://doi.org/10.1007/s10238-014-0280-y.
[61] X. Gao, et al., MiR-320a downregulation is associated with imatinib resistance in gastrointestinal stromal tumors, Acta Biochim. Biophys. Sin. 46 (1) (Jan. 2014) 72–75, https://doi.org/10.1093/abbs/gmt118.
[62] H.J. Choi, et al., MicroRNA expression profile of gastrointestinal stromal tumors is distinguished by 14q loss and anatomic site, Int. J. Cancer 126 (7) (Apr. 2010) 1640–1650, https://doi.org/10.1002/ijc.24897.
[63] W.K. Kim, et al., MicroRNA-494 downregulates KIT and inhibits gastrointestinal stromal tumor cell proliferation, Clin. Cancer Res. 17 (24) (Dec. 2011) 7584–7594, https://doi.org/10.1158/1078-0432.CCR-11-0166.
[64] T. Niinuma, et al., Downregulation of miR-186 is associated with metastatic recurrence of gastrointestinal stromal tumors, Oncol. Lett. 14 (5) (Nov. 2017) 5703–5710, https://doi.org/10.3892/ol.2017.6911.
[65] J.A. Breiner, et al., Loss of 14q and 22q in gastrointestinal stromal tumors (pacemaker cell tumors), Cancer Genet. Cytogenet. 120 (2) (Jul. 2000) 111–116, https://doi.org/10.1016/s0165-4608(00)00212-0.
[66] R. Fan, et al., microRNA-218 increase the sensitivity of gastrointestinal stromal tumor to imatinib through PI3K/AKT pathway, Clin. Exp. Med. 15 (2) (May. 2015) 137–144, https://doi.org/10.1007/s10238-014-0280-y.
[67] G.A. Calin, et al., Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers, Proc. Natl. Acad. Sci. U.S.A. 101 (9) (Mar. 2004) 2999–3004, https://doi.org/10.1073/pnas.0307323101.
[68] G. Ravegnini, G. Valori, Q. Zhang, R. Ricci, P. Hrelia, S. Angelini, Pharmacogenetics in the treatment of gastrointestinal stromal tumors - an updated review, Expet Opin. Drug Metabol. Toxicol. 16 (9) (2020) 797–808, https://doi.org/10.1080/17425255.2020.1789589.
[69] D.-H. Koo, M.-H. Ryu, B.-Y. Ryoo, et al., Association of ABCG2 polymorphism with clinical efficacy of imatinib in patients with gastrointestinal stromal tumor, Cancer Chemother. Pharmacol. 75 (2015) 173–182.
[70] M.C. Verboom, J.S.L. Kloth, J.J. Swen, et al., Genetic polymorphisms in angiogenesis-related genes are associated with worse progression-free survival of patients with advanced gastrointestinal stromal tumours treated with imatinib, Eur. J. Cancer 86 (2017) 226–232.
[71] K. Wasielewski, B. Wasag, A. Wozniak, et al., Influence of cytochrome P450, ABC and SLC gene polymorphisms on imatinib therapy outcome of patients with gastrointestinal stromal tumours (GIST), Folia Biol. (Czech Republic) 63 (2017) 78–83.
[72] G. Ravegnini, M. Nannini, V. Simeon, et al., Polymorphisms in DNA repair genes in gastrointestinal stromal tumours: susceptibility and correlation with tumour characteristics and clinical outcome, Tumour Biol. 37 (10) (2016) 13413–13423.
[73] H. Chen, J. Liu, Y. Zhou, et al., Association of hepatic nuclear factor 4 alpha gene polymorphisms with free imatinib plasma levels and adverse reactions in Chinese gastrointestinal stromal tumor patients, Ther. Drug Monit. 41 (2019) 582–590.

[74] Q. Zhang, J. Xu, Y. Qian, et al., Association of imatinib plasma concentration and single-nucleotide polymorphisms with adverse drug reactions in patients with gastrointestinal stromal tumors, Mol. Cancer Therapeut. 17 (2018) 2780–2787.
[75] G. Ravegnini, M. Urbini, V. Simeon, et al., An exploratory study by DMET array identifies a germline signature associated with imatinib response in gastrointestinal stromal tumor, Pharmacogenomics J. 19 (4) (2019) 390–400.
[76] J.S.L. Kloth, M.C. Verboom, J.J. Swen, et al., Genetic polymorphisms as predictive biomarker of survival in patients with gastrointestinal stromal tumors treated with sunitinib, Pharmacogenomics J. 18 (2018) 49–55.
[77] P. Rutkowski, E. Bylina, A. Klimczak, et al., The outcome and predictive factors of sunitinib therapy in advanced gastrointestinal stromal tumors (GIST) after imatinib failure - one institution study, BMC Cancer 12 (2012) 107.
[78] G. Ravegnini, M. Nannini, C. Zenesini, et al., An exploratory association of polymorphisms in angiogenesis-related genes with susceptibility, clinical response and toxicity in gastrointestinal stromal tumors receiving sunitinib after imatinib failure, Angiogenesis 20 (2017) 139–148.
[79] C.A. Knowlton, L.W. Brady, R.C. Heintzelman, Radiotherapy in the treatment of gastrointestinal stromal tumor, Rare Tumors 3 (4) (Oct. 2011) e35, https://doi.org/10.4081/rt.2011.e35.
[80] S. George, et al., Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: a multicenter phase II trial, J. Clin. Oncol. 30 (19) (Jul. 2012) 2401–2407, https://doi.org/10.1200/JCO.2011.39.9394.
[81] E.E. Ozkan, Radiotherapy for gastrointestinal stromal tumors, Chin. Med. J. 131 (2) (Jan. 2018) 235–240, https://doi.org/10.4103/0366-6999.222344.
[82] H. Zhang, et al., Radiotherapy in the management of gastrointestinal stromal tumors: a systematic review, Cancers (Basel) 14 (13) (Jun. 2022) 3169, https://doi.org/10.3390/cancers14133169.
[83] S.H. Kong, H.K. Yang, Surgical treatment of gastric gastrointestinal stromal tumor, J. Gastric Cancer 13 (1) (Mar. 2013) 3–18, https://doi.org/10.5230/jgc.2013.13.1.3.
[84] C.L. Corless, et al., Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial, J. Clin. Oncol. 32 (15) (May 2014) 1563–1570, https://doi.org/10.1200/JCO.2013.51.2046.
[85] L. D'Ambrosio, et al., Guideline-based follow-up outcomes in patients with gastrointestinal stromal tumor with low risk of recurrence: a report from the Italian Sarcoma Group, JAMA Netw. Open 6 (11) (Nov. 2023) e2341522, https://doi.org/10.1001/jamanetworkopen.2023.41522.
[86] A. Rammohan, et al., A gist of gastrointestinal stromal tumors: a review, World J. Gastrointest. Oncol. 5 (6) (Jun. 2013) 102–112, https://doi.org/10.4251/wjgo.v5.i6.102.PMC3708046.
[87] A. Bongiovanni, et al., Pleural effusion in a patient with metastatic gastrointestinal stromal tumor treated with imatinib: case report, Future Oncol. 10 (15) (Dec. 2014) 2423–2427, https://doi.org/10.2217/fon.14.159.
[88] S.J. Ford, A. Gronchi, Indications for surgery in advanced/metastatic GIST, Eur. J. Cancer 63 (Aug. 2016) 154–167, https://doi.org/10.1016/j.ejca.2016.05.019.
[89] G.D. Demetri, et al., Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial, Lancet 368 (9544) (Oct. 2006) 1329–1338, https://doi.org/10.1016/S0140-6736(06)69446-4.
[90] C. Lebreton, et al., Predicting severe toxicity of targeted therapies in elderly patients with cancer (PreToxE): a mul- ticenter, prospective, and retrospective study, J. Clin. Oncol. 37 (15_suppl) (May 2019) 11550, https://doi.org/10.1200/JCO.2019.37.15_suppl.11550.
[91] C. Luo, et al., Case report of a KIT-mutated melanoma patient with an excellent response to apatinib and temozolomide combination therapy, OncoTargets Ther. 14 (Sep) (2017) 4553–4557, https://doi.org/10.2147/OTT.S146409.
[92] National Comprehensive Cancer Network, GIST (version 1.2021). https://www.nccn.org/professionals/physician_gls/pdf/gist.pdf. (Accessed 6 September 2024).
[93] C. Cauchi, et al., Evaluation of nilotinib in advanced GIST previously treated with imatinib and sunitinib, Cancer Chemother. Pharmacol. 69 (4) (Apr. 2012) 977–982, https://doi.org/10.1007/s00280-011-1785-7.
[94] S. Farag, et al., Revolutions in treatment options in gastrointestinal stromal tumours (GISTs): the latest updates, Curr. Treat. Options Oncol. 21 (7) (May 2020) 55, https://doi.org/10.1007/s11864-020-00754-8.
[95] P. Schöffski, et al., Activity and safety of the multi-target tyrosine kinase inhibitor cabozantinib in patients with metastatic gastrointestinal stromal tumour after treatment with imatinib and sunitinib: European Organisation for Research and Treatment of Cancer phase II trial 1317 'CaboGIST', Eur. J. Cancer 134 (Jul) (2020) 62–74, https://doi.org/10.1016/j.ejca.2020.04.021.
[96] A.P. Garner, et al., Ponatinib inhibits polyclonal drug-resistant KIT onco- proteins and shows therapeutic potential in heavily pretreated gastrointestinal stromal tumor (GIST) patients, Clin. Cancer Res. 20 (22) (Nov. 2014) 5745–5755, https://doi.org/10.1158/1078-0432.CCR-14-1397.
[97] M.C. Heinrich, et al., Crenolanib inhibits the drug- resistant PDGFRA D842V mutation associated with imatinib- resistant gastrointestinal stromal tumors, Clin. Cancer Res. 18 (16) (Aug. 2012) 4375–4384, https://doi.org/10.1158/1078-0432.CCR-12-0625.
[98] U. Kefeli, et al., Efficacy of sorafenib in patients with gastrointestinal stromal tumors in the third- or fourth-line treatment: a retrospective multicenter experience, Oncol. Lett. 6 (2) (Aug. 2013) 605–611, https://doi.org/10.3892/ol.2013.1408.
[99] J. Vadakara, M. von Mehren, Gastrointestinal stromal tumors: management of metastatic disease and emerging therapies, Hematol. Oncol. Clin. N. Am. 27 (5) (Oct. 2013) 905–920, https://doi.org/10.1016/j.hoc.2013.07.007.
[100] T. Miyoshi, et al., Efficacy of erlotinib and imatinib in a patient with a rectal gastrointestinal stromal tumor and synchronous pulmonary adenocarcinoma: a case report, J. Med. Invest. 63 (1–2) (2016) 144–148, https://doi.org/10.2152/jmi.63.144.
[101] S. Gabellone, et al., Lignin nanoparticles deliver novel thymine biomimetic photo-adducts with antimelanoma activity, Int. J. Mol. Sci. 23 (2) (Jan. 2022) 915, https://doi.org/10.3390/ijms23020915.
[102] E. Capecchi, et al., Biosynthesis of novel ascorbic acid esters and their encapsulation in lignin nanoparticles as carriers and stabilizing systems, Int. J. Mol. Sci. 24 (10) (May 2023) 9044, https://doi.org/10.3390/ijms24109044.
[103] D. Piccinino, et al., Lignin nanoparticles as sustainable photoprotective carriers for sunscreen filters, ACS Omega 7 (42) (Oct. 2022) 37070–37077, https://doi.org/10.1021/acsomega.2c02133.
[104] O.S. Fetzer, et al., Cyclodextrin-based polymers for therapeutic delivery. https://pubchem.ncbi.nlm.nih.gov/patent/WO-2012145632-A1, 2012. (Accessed 6 September 2024).
[105] S. Hong, J.W. Bae, Amphiphilic dendron-coils, micelles thereof and uses. https://pubchem.ncbi.nlm.nih.gov/patent/WO-2012116073-A2, 2012. (Accessed 6 September 2024).
[106] L. Sun, et al., Smart nanoparticles for cancer therapy, Signal Transduct. Targeted Ther. 8 (1) (Nov. 2023) 418, https://doi.org/10.1038/s41392-023-01642-x.
[107] C. Li, M. Zhou, R. Zhang, Multifunctional chelator-free radioactive nanoparticles for imaging and therapy. https://pubchem.ncbi.nlm.nih.gov/patent/WO-2012138379-A2, 2012. (Accessed 6 September 2024).
[108] S. Schötz, et al., Esterase-responsive polyglycerol-based nanogels for intracellular drug delivery in rare gastrointestinal stromal tumors, Pharmaceuticals 16 (11) (Nov. 2023) 1618, https://doi.org/10.3390/ph16111618.
[109] E. Capecchi, et al., Nanoparticles of lignins and saccharides from fishery wastes as sustainable UV-shielding, antioxidant, and antimicrobial biofillers, Biomacromolecules 23 (8) (Aug. 2022) 3154–3164, https://doi.org/10.1021/acs.biomac.2c00236.
[110] J. Prados, et al., Application of nanotechnology in the treatment and diagnosis of gastrointestinal cancers: review of recent patents, Recent Pat. Anti-Cancer Drug Discov. 9 (1) (Jan. 2014) 21–34, https://doi.org/10.2174/1574891x113089990039.
[111] V. Gigli, et al., Tuning the effect of chitosan on the electrochemical responsiveness of lignin nanoparticles, ACS Biomater. Sci. Eng. 9 (6) (Jun. 2023) 3597–3605, https://doi.org/10.1021/acsbiomaterials.2c01494.
[112] E. Tomaino, E. Capecchi, D. Piccinino, R. Saladino, Lignin nanoparticles support lipase-tyrosinase enzymatic cascade in the synthesis of lipophilic hydroxytyrosol ester derivatives, ChemCatChem 14 (2022) 18, https://doi.org/10.1002/cctc.202200380.
[113] R. Augustine, N. Kalva, H.A. Kim, Y. Zhang, I. Kim, pH-responsive polypeptide-based smart nano-carriers for theranostic applications, Molecules 24 (16) (Aug. 2019) 2961, https://doi.org/10.3390/molecules24162961.

[114] J. Prados, et al., Application of nanotechnology in the treatment and diagnosis of gastrointestinal cancers: review of recent patents, Recent Pat. Anti-Cancer Drug Discov. 9 (1) (Jan. 2014) 21–34, https://doi.org/10.2174/1574891x113089990039.
[115] K. Unnikrishnan, L.V. Thomas, R.M. Ram Kumar, Advancement of scaffold-based 3D cellular models in cancer tissue engineering: an update, Front. Oncol. 11 (Oct. 2021) 733652, https://doi.org/10.3389/fonc.2021.733652.
[116] Y.J. Kim, H.I. Bae, O.K. Kwon, M.S. Choi, Three-dimensional gastric cancer cell culture using nanofiber scaffold for chemosensitivity test, Int. J. Biol. Macromol. 45 (1) (Jul. 2009) 65–71, https://doi.org/10.1016/j.ijbiomac.2009.04.003.
[117] J. Kim, J. Jang, D.W. Cho, Controlling cancer cell behavior by improving the stiffness of gastric tissue-decellularized ECM bioink with cellulose nanoparticles, Front. Bioeng. Biotechnol. 9 (Mar. 2021) 605819, https://doi.org/10.3389/fbioe.2021.605819.
[118] J.H. Sung, J. Yu, D. Luo, M.L. Shuler, J.C. March, Microscale 3-D hydrogel scaffold for biomimetic gastrointestinal (GI) tract model, Lab Chip 11 (3) (Feb. 2011) 389–392, https://doi.org/10.1039/c0lc00273a.
[119] A. Jefremow, M.F. Neurath, Nanoparticles in gastrooncology, Visc Med 36 (2) (Apr. 2020) 88–94, https://doi.org/10.1159/000506908.
[120] L. Mercatali, S. Vanni, G. Miserocchi, C. Liverani, C. Spadazzi, The emerging role of cancer nanotechnology in the panorama of sarcoma, Front Bioeng Biotechnol 10 (2022). https://doi.org/10.3389/fbioe.2022.953555.