Review
NT157 as an Anticancer Drug Candidate That Targets Kinase- and Phosphatase-Mediated Signaling

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Abstract: Cancer, characterized by uncontrolled cell growth and metastasis, represents a significant challenge to public health. The IGF1/IGF1R axis plays a pivotal role in tumor proliferation and survival, presenting an attractive target for intervention. NT157, a small molecule tyrphostin, has emerged as a promising inhibitor of this axis, displaying potent antineoplastic effects across various cancer types. This review synthesizes the literature on NT157’s mechanism of action and its impact on cellular processes in experimental cancer models. Initially identified for inducing the serine phosphorylation of IRS1 and IRS2, leading to their degradation and inhibiting the IGF1R signaling cascade, subsequent studies revealed additional targets of NT157, including STAT3, STAT5, and AXL, suggesting a multifaceted mechanism. Experimental evidence demonstrates that NT157 effectively suppresses tumor growth, metastasis, and angiogenesis in diverse cancer models. Additionally, NT157 enhances chemotherapy efficacy in combination therapy. Moreover, NT157 impacts not only tumor cells but also the tumor microenvironment, modulating inflammation and immune responses by targeting cancer-associated fibroblasts, myeloid cells, and immune cells, creating a suppressive milieu hindering tumor progression and metastasis. In conclusion, NT157 exhibits remarkable versatility in targeting multiple oncogenic pathways and hallmarks of cancer, underscoring its potential as a promising therapeutic agent.

Keywords: NT157; kinases; phosphatases; antineoplastic agents; cell signaling

1. Introduction

According to the U.S. National Cancer Institute (NCI)’s definition, cancer is a disease in which some of the body’s cells grow uncontrollably and spread to other parts of the body, but there is growing evidence that this disease arises from preneoplastic molecular lesions that culminate in transformed cells subject to evolution by natural selection [1]. Cancer comprises a heterogeneous set of diseases that stand as a pervasive contributor to morbidity and mortality in the Western world, ranking as the second leading cause of death following cardiovascular disease. It remains one of the paramount challenges in public health today [2]. In 2000, Hannah and Weinberg introduced the initial hallmarks of cancer, comprising six characteristics [3] which were subsequently expanded to ten characteristics in 2011 [4] and further revised in 2022 [5]. Currently, fourteen hallmarks of cancer are described, which include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, genome instability/mutation, inducing/accessing vasculature, activating invasion and metastasis, tumor-promoting inflammation, deregulating cellular metabolism, avoiding immune destruction, unlocking phenotypic plasticity, non-mutational epigenetic reprogramming, senescent cells, and polymorphic microbiomes [5]. Significant progress has been made in understanding the cellular and molecular foundations underlying cancer hallmarks. This has led to the elucidation of
various signaling pathways involved, which have subsequently become targets for therapeutic interventions. Such interventions have reshaped the natural course of numerous malignant neoplasms, marking a transformative advancement in cancer treatment.

As previously mentioned, sustained growth stands as a characteristic trait of tumors. Growth factors serve to stimulate both cancer cells and stromal cells, fostering proliferation, migration, and invasion. This, in turn, fuels tumor expansion, angiogenesis, and metastasis. Insulin-like growth factors (IGF) are crucial contributors to mammalian growth, development, aging, and disease progression. Deficiency in IGF may hinder development and lead to metabolic issues, while elevated IGF levels are inversely correlated with longevity and positively correlated with the risk of cancer. IGF is primarily synthesized by the liver, as well as by tumor cells and cancer-associated macrophages, and exerts its functions through its receptor, insulin-like growth factor receptor (IGFR) [6,7].

In the field of oncology, the insulin-like growth factor 1/insulin-like growth factor 1 receptor (IGF1/IGF1R) axis stands out as one of the most extensively studied pathways [8,9]. From a molecular point of view, IGF1 binds to IGF1R, triggering its intracellular kinase activity. This activation, in turn, stimulates insulin receptor substrates 1 (IRS1) and 2 (IRS2). Subsequently, IRS1 and IRS2 play pivotal roles in regulating the transcription of downstream genes and modulating cell physiology by activating the RAS/RAF/MAPK and PI3K/AKT/mTOR signaling pathways [10–12]. The most well-known members of the MAPK family are ERK1 and ERK2. Once activated, ERK phosphorylates various proteins in the cell, including transcription factors, leading to changes in gene expression and cellular responses such as proliferation, differentiation, and survival [13]. The PI3K/AKT/mTOR pathway is another vital signaling pathway within cells that regulates various cellular processes, including cell growth, proliferation, survival, and metabolism [14].

An aberrant expression of IGF1R and the autocrine production of IGF1 have been reported in several tumors (reviewed in [15]). Consequently, this signaling axis has garnered attention as a potential target for pharmacological inhibition. Indeed, selective inhibitors have been developed, employing strategies ranging from the neutralizing antibodies to IGF1 to inhibitors of IGF1R activity [15]. However, clinical studies consistently indicate that the effectiveness of a strategy targeting the IGF1/IGF1R axis is likely to be limited to a small subset of patients due to various escape and resistance mechanisms [16,17]. Therefore, current efforts are focused on seeking rational combination strategies that include IGF1/IGF1R inhibitors [16].

In addition to activation by the insulin receptor (IR) and IGF1R, IRS1 has been demonstrated to undergo phosphorylation due to the growth hormone receptor (GHR) and the ERBB family of tyrosine kinase receptors independent of IGF1R [18]. Additionally, other proteins with oncogenic potential, such as proinflammatory cytokines and anaplastic lymphoma receptor tyrosine kinase, may also activate IRS1, which suggests that IRS1 may serve as an escape mechanism and play a significant role in resistance to IGF1R inhibitors [18]. Thus, acting directly on the inhibition of IRS proteins could be a promising strategy to avoid intrinsic and acquired resistance.

Another tyrosine kinase receptor worth highlighting is AXL, a member of the TAM (TYRO3, AXL, and MERTK) family of receptors, which is also involved in various relevant cellular processes. The primary ligand for AXL is growth-arrest-specific protein 6 (GAS6). The binding of GAS6 to the extracellular domain of AXL induces dimerization (or oligomerization), which leads to kinase domains trans-phosphorylating each other on specific tyrosine residues and brings the intracellular kinase domains into close proximity. Once activated, AXL initiates several downstream signaling cascades, including PI3K/AKT/mTOR, MAPK, and JAK/STAT [19–21].

NT compounds are small molecule tyrphostins that were developed during the search for IGF1R kinase inhibitors. Among the members of this group of compounds, we can mention NT52, NT75, NT157, and NT205 [22]. Tyrphostins (short for “tyrosine phosphorylation inhibitors”) are a class of synthetic compounds that inhibit tyrosine kinases by competing with ATP to bind to the kinase’s active site [23]. By blocking ATP binding, tyrphostins
prevent the phosphorylation of tyrosine residues on substrate proteins, thereby disrupting downstream signaling pathways that are essential for various cellular processes [24]. Some tyrphostins have significant implications in cancer therapy and other diseases where tyrosine kinase signaling is dysregulated. Notable examples include AG-1478 (an EGFR inhibitor), AG-490 (a JAK inhibitor), and AG-1296 (a PDGFR inhibitor) [25–27].

Unlike classic tyrphostins, NT compounds exhibit non-competitive ATP as well as substrate non-competitive inhibition of the full-length IGF1R without inhibiting the isolated kinase domain of the receptor, suggesting an allosteric inhibition [22]. During the generation of NT compounds, modifications that impact the structure–activity relationship and deserve to be highlighted include the conversion of amide to thioamide, the substitution of a phenyl group with a catecholic ring, the substitution of a phenolic group at the 5′ position of the aminobenzyl moiety in all active NT compounds [22]. The most promising prototype of this class was NT157, and its chemical structure is illustrated in Figure 1.

![NT157 chemical structure](image)

Figure 1. Representation of the NT157 chemical structure. CAS, Chemical Abstracts Service.

The aim of this review is to comprehensively explore the literature concerning the mechanism of action of NT157, elucidating its molecular and cellular effects within experimental cancer models. Additionally, it aims to suggest potential avenues for future research.

2. Molecular Targets of NT157

The initial mechanism of action described for NT157 involves the induction of serine phosphorylation of IRS1 and IRS2 proteins, resulting in their degradation and the suppression of the IRS/IGF1R axis. In this model, NT157 binds to an allosteric site on IGF1R, prompting a conformational change that leads to the dissociation of IRS1 or IRS2 from the receptor. Consequently, the receptor exhibits a stronger interaction with the adapter protein SHC, activating C-RAF and enhancing signaling to ERK1/2. Subsequently, cytoplasmic IRS1/2 undergoes extensive serine phosphorylation mediated by ERK1/2. Ultimately, serine phosphorylation targets IRS1 and IRS2 for degradation by the proteasome, resulting in prolonged IGF1R inhibition [22]. However, even in the context of ERK1/2 inhibition by PLX-4032, IRS1 and IRS2 proteins had attenuated but not completely inhibited serine phosphorylation levels, indicating knowledge gaps in the initial model [28]. Later, a proteomics study indicated other targets of NT157, including p38MAPK, JNK, and AXL [29]. Focusing on p38MAPK and JNK, as well as ERK, these proteins belong to the MAPK family and are capable of phosphorylating IRS proteins at serine sites [30,31]. Studies using cells confirmed that NT157 strongly induces the activation of JNK1/2 and that the pharmacological inhibition of JNK (SP600125) reduces the serine phosphorylation of IRS1 and IRS2, identifying another MAPK involved in the mechanism of action of NT157 in addition to ERK1/2 [32]. Similarly, the pharmacological inhibition of p38MAPK (SB203580) significantly mitigated the antiproliferative effect of NT157. However, its impact on the phosphorylation of IRS proteins has not been investigated so far [29].

Among the various experimental models investigated, the inhibition of IRS proteins alone does not account for all the attributed antineoplastic effects of NT157. Consequently,
other targets of NT157 have been identified, namely STAT3, STAT5, and AXL. The inhibition of STAT3 and STAT5 occurs independently of IRS protein inhibition and is linked to the activation of protein phosphatases [28,33]. Additionally, NT157 has been associated with the decreased expression and activation of AXL, a significant receptor tyrosine kinase linked to chemoresistance in cancer [32]. The mechanism by which NT157 reduces AXL is still a point of debate. In melanoma models, AXL protein expression is decreased without concurrent changes in AXL mRNA levels [29]. Conversely, in lung cancer, the decrease in AXL protein expression is correlated with a reduction in AXL mRNA levels [32]. Thus, it has been widely accepted that NT157 exerts its antineoplastic activity by acting on multiple targets of interest in oncology, making it a drug with unique properties. A model for the mechanism of action of NT157 is presented in Figure 2.

![Proposed model for the multitarget mechanism of action of NT157](Figure 2. Proposed model for the multitarget mechanism of action of NT157. IGF1 binds to and activates IGF1R, resulting in the recruitment and tyrosine phosphorylation (pY) of the IRS1/2 adapter proteins and the activation of downstream pathways associated with cell growth and survival, including PI3K/AKT/mTOR. NT157 binds to an allosteric site on IGF-1R, inducing a conformational change that leads to the dissociation of IRS1/2 from the receptor, allowing interaction with the adapter protein SHC. SHC then leads to the activation of ERK1/2, which phosphorylates IRS1/2 at serine sites (pS). Subsequently, serine-phosphorylated IRS1/2 is targeted for degradation by the proteasome, impairing the IGF1R signaling. Through mechanisms that are still poorly understood, NT157 leads to the activation of JNK1/2, another member of the MAPK family, which also phosphorylates IRS1/2 at serine sites and leads to their degradation. Additionally, NT157 can reduce the activation and expression of AXL, an important receptor associated with the activation of the PI3K/AKT/mTOR, MAPK, and JAK/STAT pathways. Furthermore, NT157 activates protein phosphatases (PPs) whose mechanisms are not yet fully elucidated, inhibiting the activity of STAT3 and STAT5 proteins. This inhibition prevents their nuclear translocation and the activation of target genes. Figure created by Biorender.

3. Impact of NT157 on Cellular Processes in Experimental Cancer Models

The initial studies exploring the impact of NT157 on cellular processes commenced with investigations into melanoma cells. Researchers observed a notable reduction in
viability and migration in vitro, coupled with diminished tumor growth and lung metastasis in a xenotransplanted murine model utilizing A375 melanoma cells [22]. Subsequent research by the same group unveiled further insights, demonstrating that NT157 mitigates in vitro angiogenesis and the secretion of pro-angiogenic and pro-invasion factors in xenotransplanted tumors derived from A375SM cells [28]. In uveal melanoma, a rare subtype characterized by limited therapeutic options [34], NT157 also exhibited significant efficacy, diminishing cell growth, survival, migration, and in vivo tumor expansion [35].

These promising outcomes extend beyond melanoma, as evidenced by similar findings in various solid tumors, including prostate cancer [36], osteosarcoma [37], colorectal cancer [38], renal cell carcinoma [39], breast cancer [40–44], gastric cancer [45], hepatocellular carcinoma [46], lung cancer [32,47], glioma [48], and ovarian cancer [49]. Across these studies, NT157 treatment consistently attenuated the malignant phenotype of cancer cells, evidenced by reduced proliferation, survival, clonal growth, migration, invasion, and/or cell cycle progression. Moreover, it often induced apoptosis or autophagy.

In hematological malignancies, including acute lymphoblastic leukemia [50], myeloproliferative neoplasm [33,51], chronic myeloid leukemia [52,53], and multiple myeloma [54], NT157 also demonstrated remarkable antineoplastic effects. Notably, NT157 exhibited efficacy even in chronic myeloid leukemia models harboring the BCR::ABL1 T315I mutation [52], which confers resistance or partial resistance to most currently employed clinically tyrosine kinase inhibitors [55]. A comprehensive overview of the cancer models and the cellular responses triggered by NT157 are depicted in Table 1.

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Experimental Models</th>
<th>NT157’s Potency</th>
<th>NT157’s Molecular Targets</th>
<th>NT157’s Cellular Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>Multiple models *</td>
<td>IC_{50}: 0.3–1 µM (72 h)</td>
<td>IRS1 and IRS2</td>
<td>Reduction in in vitro cell viability and migration, as well as in vivo tumor growth and lung metastasis.</td>
<td>[22]</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>LNCaP, PC3, and normal prostatic fibroblasts</td>
<td>IC_{50}: 1.4–2.5 µM (72 h)</td>
<td>IRS1 and IRS2</td>
<td>Reduction in cell viability, cell cycle arrest, and in vivo tumor growth.</td>
<td>[36]</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>U-2OS, O519, and MG-63 cells</td>
<td>IC_{50}: 0.3–0.8 µM (72 h)</td>
<td>IRS1 and IRS2</td>
<td>Reduction in cell proliferation and cell cycle.</td>
<td>[37]</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Multiple models **</td>
<td>IC_{50}: 0.28 µM (72 h)</td>
<td>IRS1, IRS2, and STAT3</td>
<td>Reduction in cell viability and angiogenesis.</td>
<td>[28]</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>HCT-116, SW620, HT-29, SW4-80, DLD-1, and MC-38 cells</td>
<td>Not determined</td>
<td>IRS1, IRS2, and STAT3</td>
<td>Reduction in cell migration, in vivo tumor growth, and metastasis.</td>
<td>[38]</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>A-498, ACHN, Caki-1, Caki-2 77, and 786-O cells</td>
<td>Not determined</td>
<td>IGF1 signaling and STAT3</td>
<td>Attenuation in IGF1-induced cell proliferation.</td>
<td>[39]</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>4T1 and Ei0771 cells</td>
<td>Not determined</td>
<td>IRS1</td>
<td>Reduction in in vivo metastasis.</td>
<td>[40]</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>MCF 10A cells</td>
<td>Not determined</td>
<td>IRS1</td>
<td>Reduction in 3D cell proliferation.</td>
<td>[41]</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>SGC-7901 cells</td>
<td>Not determined</td>
<td>IGF1 signaling and STAT3</td>
<td>Reduction in cell proliferation and invasion.</td>
<td>[45]</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>MCF7, T-47D, and MDA-MB-231 cells</td>
<td>Not determined</td>
<td>IRS1 and IRS2</td>
<td>Reduction in cell proliferation and colony formation.</td>
<td>[42]</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>Jurkat, MOLT-4, Namalwa, Raji, and primary leukocytes from healthy donors and ALL patients</td>
<td>IC_{50}: 0.3–1.9 µM (72 h)</td>
<td>IGF1R and IRS1</td>
<td>Reduction in cell viability, proliferation, migration, and induction of cell cycle arrest and apoptosis.</td>
<td>[50]</td>
</tr>
<tr>
<td>Cancer Type</td>
<td>Experimental Models</td>
<td>NT157’s Potency</td>
<td>NT157’s Molecular Targets</td>
<td>NT157’s Cellular Effects</td>
<td>Reference</td>
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<tr>
<td>Myeloproliferative neoplasm</td>
<td>HEL, SET-2, and primary cells from MPN patients</td>
<td>IC_{50}: 0.68–&gt;3.2 μM (72 h)</td>
<td>IRS1, IRS2, STAT3, and STAT5</td>
<td>Reduction in cell viability, proliferation, clonal growth, and induction of cell cycle arrest and apoptosis.</td>
<td>[33]</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>K-562, Ba/F3 expressing BCR::ABL1 and BCR::ABL1T315I, and primary cells from CML patients.</td>
<td>IC_{50}: 0.3–0.68 μM (48 and 72 h)</td>
<td>IRS1 and IRS2</td>
<td>Reduction in cell viability, proliferation, clonal growth, and induction of cell cycle arrest and apoptosis.</td>
<td>[52]</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>MCF7 and T-47D</td>
<td>Not determined</td>
<td>IRS1</td>
<td>Reduction in clonal growth.</td>
<td>[43]</td>
</tr>
<tr>
<td>Uveal Melanoma</td>
<td>Mel20–06–039, OMM-1, Mel202, 92–1, Mel270g, MM28, MP38, MPH1, BJ fibroblasts, HaCaT, and HEMn cells</td>
<td>Not determined</td>
<td>IRS1 and IRS2</td>
<td>Reduction in vitro cell growth, survival, and migration, as well as in vivo tumor growth.</td>
<td>[35]</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>NCI-H1299, NCI-H460, and NCI-H1975 cells</td>
<td>IC_{50}: 1.8–4.8 μM (72 h)</td>
<td>IRS1, IRS2, JNK, and AXL</td>
<td>Reduction in cell viability, clonal growth, migration, and induction of cell cycle arrest and apoptosis.</td>
<td>[32]</td>
</tr>
<tr>
<td>Myeloproliferative neoplasm</td>
<td>Ba/F3 expressing JAK2V617F cells</td>
<td>IC_{50}: 0.8 μM (48 h)</td>
<td>IRS1, IRS2, STAT3, and STAT5</td>
<td>Reduction in cell viability, proliferation, and induction of apoptosis.</td>
<td>[51]</td>
</tr>
<tr>
<td>Ciona</td>
<td>U-87 MG and U-251 MG cells</td>
<td>IC_{50}: &gt;40 μM (24 h)</td>
<td>STAT3</td>
<td>Reduction in cell viability, survival, cell cycle progression, and migration, as well as in vivo tumor growth.</td>
<td>[48]</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>K-562 cells</td>
<td>Not determined</td>
<td>IRS2</td>
<td>Inhibition of erythroid differentiation induced by hypoxia.</td>
<td>[53]</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>MCF7 and T-47D</td>
<td>Not determined</td>
<td>IRS1</td>
<td>Reduction in cell proliferation.</td>
<td>[44]</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>OVCAR-3 and OVCA433 cells</td>
<td>IC_{50}: &gt;3.2 μM (24 h)</td>
<td>IRS1 and IRS2</td>
<td>Reduction in cell viability, proliferation, clonal growth, and induction of apoptosis and autophagy.</td>
<td>[49]</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>MM.1S, MM.1R, U266, and RPMI 8226 cells</td>
<td>IC_{50}: 2.6–18.5 μM (72 h)</td>
<td>IRS2, STAT3, and STAT5</td>
<td>Reduction in cell viability, clonal growth, and induction of cell cycle arrest and apoptosis.</td>
<td>[54]</td>
</tr>
</tbody>
</table>

* A-375 (melanoma), HCT-116 (colon cancer), HCT-15 (colon cancer), SK-ES-1 (Ewing sarcoma), NCI-H460 (lung cancer), HepG2 (hepatocarcinoma), DU-145 (prostate cancer), YUMAC, YURIF, YUSIK (melanoma), M571, M2068, M560n (melanoma), normal melanocytes, and normal fibroblasts; ** A-375 (melanoma), DU145 (prostate cancer), MCF7 (breast cancer), SK-BR-3 (breast cancer), RPMI 8226 (multiple myeloma), SK-ES-1 (Ewing sarcoma), YUMAC, YUSIK, M571, M2068 (patient-derived melanoma) cells. Abbreviations: IC_{50}, half-maximal inhibitory concentration; MPN, myeloproliferative neoplasm; CML, chronic myeloid leukemia. Genes and proteins are reported according to the HUGO Gene Nomenclature Committee.

In drug combination assays, NT157 enhances the response to various chemotherapy agents: docetaxel in prostate cancer [36]; everolimus, NVP-BEZ235, doxorubicin, cisplatin,
and methotrexate in osteosarcoma [37]; rapamycin and metformin in breast cancer [42,43]; gefitinib in lung cancer [32]; and TRAIL in glioma [48].

4. Targeting the Tumor Microenvironment with NT157

In addition to acting directly on tumor cells, there is evidence that NT157 acts on cells in the tumor microenvironment that support the development of cancer progression. In a colorectal cancer model, it was reported that NT157 acts on cancer-associated fibroblasts and myeloid cells, favoring a suppressive tumor microenvironment and reducing inflammation through the modulation of chemokines and growth factors, such as IL-6, IL-11, IL-23, CCL2, CCL5, CXCL7, CXCL5, ICAM1, and TGFβ [38].

In an experimental metastasis model, NT157 exhibited a reduction in tumor weight and lung metastasis in mice with comparable primary tumor weights, indicating a direct impact of NT157 on metastasis. NT157 treatment also led to the decreased expression of ARG1, TGFβ1, and IL-10 in Gr-1+ CD11b+ cells. Furthermore, in tumor-bearing mice treated with NT157, the depletion of CD8+ T cells attenuated some of the inhibitory effects of NT157 on metastasis and primary tumor size. However, this reduction in metastasis did not reach the level observed with CD8 depletion alone, indicating a direct tumor effect of NT157 in addition to its impact on the host immune response [40]. Collectively, these findings show that NT157 attenuates not only tumor growth but also immune suppression, which it is associated with the inhibition of metastasis.

5. Conclusions and Future Directions

Considering the limited efficacy observed with IGF1/IGF1R inhibitors in clinical trials and the potential role of IRS proteins in escaping the inhibition of the IGF1/IGF1R axis through activation by other receptors, as well as the necessity for combined therapies to forestall resistance, NT157 emerges as a highly compelling pharmacological prototype. NT157 acts directly by inducing the degradation of IRS1 and IRS2 proteins. Moreover, it targets multiple key proteins in oncology, including STAT3, STAT5, and AXL.

The JAK/STAT pathway plays a critical role in regulating the immune system and inflammation, but the dysregulation of this pathway is also frequently associated with cancer. The aberrant activation of JAK/STAT signaling can promote cancer cell proliferation, survival, angiogenesis, and metastasis, while also suppressing antitumor immune responses. Several genetic alterations and mutations in components of the JAK/STAT pathway have been identified in various cancers, including leukemia, lymphoma, and solid tumors [56,57]. As a result, targeting the JAK/STAT pathway has emerged as a promising therapeutic strategy for cancer treatment. In fact, several JAK inhibitors have been developed and approved for the treatment of certain cancers, particularly hematologic malignancies. Ongoing research continues to explore the potential of targeting this pathway in various cancer types and identifying predictive biomarkers to guide treatment decisions [58,59].

AXL signaling contributes to various hallmarks of cancer, including the promotion of cell proliferation, survival, epithelial–mesenchymal transition (EMT), angiogenesis, and metastasis [60,61]. Additionally, AXL activation can suppress antitumor immune responses by modulating immune cell function and promoting immune evasion. Due to its role in promoting cancer progression and therapy resistance, AXL has emerged as a potential therapeutic target in cancer treatment. Inhibitors targeting AXL signaling are being investigated in preclinical and clinical studies, either as single agents or in combination with other therapies, with the aim of inhibiting tumor growth and metastasis and overcoming therapy resistance [62–65].

Another experimental aspect that deserves highlighting is that in several experimental models, the effects of NT157 persist even after a short exposure followed by a washout to remove the drug. These findings are evident through the phosphorylation of IRS1/2 and STAT3 proteins [28], as well as the impact on colony formation [32]. These data suggest that the drug could have a favorable pharmacodynamic and pharmacokinetic profile, as a
short exposure period might be sufficient to maintain a prolonged pharmacological effect. However, future functional studies are necessary to define the minimum exposure time to NT157 required for significant impacts on the cellular phenotype.

In summary, due to the versatility of NT157 in suppressing multiple oncogenic pathways, the relevant inhibition of several hallmarks of cancer in preclinical models has been reported, including the reduction of proliferative signaling, the activation of invasion and metastasis, the accessing of vasculature (angiogenesis), tumor-promoting inflammation, and the induction of cell death (by apoptosis and autophagy) (Figure 3). Future research should focus on determining NT157’s clinical effectiveness and investigating combination approaches to overcome resistance. Understanding its efficacy in clinical settings is vital for practical use and to improve patient outcomes. By thoroughly examining these areas, research can advance NT157’s development as a promising cancer therapy.

Figure 3. Cellular mechanisms impacted by NT157 in preclinical cancer models. NT157 exerts a multifaceted impact on cellular processes crucial in cancer progression. It effectively inhibits proliferation [33,42], cell cycle progression [37,50], and clonal expansion [52] while concurrently suppressing migration [22], invasion, and angiogenesis [28]. These collective effects limit tumor cell access to the vasculature, thereby impeding metastasis [40]. Notably, NT157 retains its efficacy in inducing programmed cell death mechanisms such as apoptosis and autophagy [49,54]. Moreover, by modulating the tumor microenvironment, NT157 mitigates tumor-promoting inflammation [38,40]. Consequently, NT157 emerges as a promising therapeutic candidate for attenuating both the development and progression of tumors. Figure created by Biorender.

Author Contributions: Conceptualization and writing: K.L. and J.A.M.-N.; image: J.A.M.-N.; editing, K.L. and J.A.M.-N. All authors have read and agreed to the published version of the manuscript.

Funding: K.L. received a fellowship from the São Paulo Research Foundation (FAPESP) (grant 2020/12842-0). This study was supported by grant 2021/11606-3 from FAPESP. This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Brasil (CAPES), Finance Code 001.

Conflicts of Interest: The authors declare no conflicts of interest.
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