Therapeutic targeting of STAT3 pathways in pancreatic adenocarcinoma: A systematic review of clinical and preclinical literature

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Abstract

Background/Objectives
Pancreatic ductal adenocarcinoma is a highly lethal disease with increasing incidence. Due to high resistance, chemo/radiotherapy has limited success in pancreatic cancer and only marginally prolongs patient survival. Therefore, novel biomarkers and therapeutic targets are needed. In the present review, we performed a comprehensive summary of therapeutic approaches targeting the GP130/JAK/STAT3 pathway.

Methods
We systematically reviewed the PubMed and Embase databases for preclinical and clinical studies, from inception to October 4, 2020, on drugs targeting the GP130/JAK/STAT3 pathway. Bias assessments and qualitative analyses were performed.

Results
Twenty-five preclinical and nine clinical trials were included in the review. All preclinical studies reported a favorable outcome in terms of pancreatic ductal adenocarcinoma progression. Furthermore, drugs targeting the GP130/JAK/STAT3 pathway were shown to be efficient chemosensitizers. However, high publication bias was assumed. In the clinical setting, bazedoxifene and itacitinib improved patient outcomes.

Conclusion
Preclinical studies strongly suggest significant efficacy of drugs targeting GP130/JAK/STAT3 in the treatment of pancreatic ductal adenocarcinoma and that these molecules are effective chemosensitizers. Though only a few trials have shown the efficacy in a clinical setting, the STAT3 pathway remains a promising drug target for future treatment of pancreatic ductal adenocarcinoma and may help overcome chemotherapy resistance.
Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal disease with increasing incidence. In most cases, pancreatic cancer presents at an advanced stage, with only 20% of all cases undergoing surgical resection. In terms of prognostic outcomes for patients, pancreatic adenocarcinoma ranks last, with an overall 5-year survival rate of 2–9% [1, 2]. Even though the management of pancreatic adenocarcinoma is evolving with the introduction of novel surgical techniques and medical therapies, only minor improvements in outcomes have been achieved. Due to high resistance, chemotherapy and radiotherapy have limited success in metastatic PDAC and only marginally prolong patient survival [3]. Current treatment options for metastatic PDAC are modified FOLFIRINOX/FOLFIRINOX or nab-paclitaxel and gemcitabine in patients with good performance status, and gemcitabine with or without a second agent for those with poor performance status [4]. Most recently, trials studying the update of immunotherapy in PDAC were negative except in a subgroup of adenocarcinoma with microsatellite instability [5].

Considering the lack of effective treatment, the identification of novel biomarkers and therapeutic targets is fundamental to developing new treatment strategies and improving clinical outcomes. Recent studies suggest that signaling pathways involving STAT3 play a key role in tumorigenesis, progression and drug resistance in several human malignancies such as leukemia, lymphomas as well as solid tumors such as hepatocellullar carcinoma, esophageal, lung, prostate, bladder and breast cancer [6, 7]. Animal models of PDAC have shown that STAT3 is an important regulator of stem cell self-renewal and cancer cell survival [8, 9]. Upregulation of STAT3 has been shown to promote the development of PDAC from pancreatic intraepithelial neoplasia [10, 11], as well as pro-metastatic niche formation in the liver [12]. Furthermore, STAT3 has been shown to mediate resistance to chemotherapy and to be associated with adverse outcomes following resection of PDAC with curative intent [13–15].

As illustrated in Fig 1, IL-6-type cytokines (IL-6, IL-10, IL-11, Leukemia inhibitory factor (LIF), Cardiotrophin-1 (CT-1), Oncostatin-M (OSM), Ciliary neurotrophic factor (CNTF)), bind glycoprotein-130 (GP130) and activate janus kinase (JAK), which in turn phosphorylates STAT3, among other signaling mediators in PDAC tumor cells as well as cells of tumor microenvironment (TME) [16]. TME in PDAC is a complex system which consists, along with extensive stromal networks, of different cell components such as pancreatic stellate cells (PSCs), cancer associated fibroblasts (CAFs), tumor associated macrophages (TAMs), mast cells, regulatory T-cells and myeloid derived suppressor cells (MDSCs), synergizing to support tumor progression, immune evasion and metastatic spreading. Interactions between different cells within the TME are mediated through signaling molecules such as STAT3 activation via IL-6-type cytokines. For instance, PDAC tumor cells can stimulate immune cells to secrete IL-6-type cytokines, supporting the development of immunosuppressive TAMs and MDSCs as well as the activation of PSCs and CAFs, which in turn induce the secretion of inflammatory cytokines through positive feedback loops [11, 17–22]. Thus, STAT3 activation drives immune cells towards immunosuppressive phenotype by inhibiting regulatory T-cells, which in turn sustains tumor immune evasion. Furthermore, the phosphorylation of STAT3 leads to enhanced transcription of downstream target genes, which promote angiogenesis, invasion, and epithelial-mesenchymal transition (EMT) [23].

Accordingly, pathways involving STAT3 appear to be promising drug targets for the treatment of PDAC. In particular, IL-6 has been shown to be a potentially efficient therapeutic approach for overcoming chemotherapy resistance. The purpose of this study was to provide a comprehensive summary of therapeutic approaches targeting the GP130/JAK/STAT3 pathway in pancreatic adenocarcinoma through a systematic qualitative review of the literature.
Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [24]. Studies were identified by searching PubMed using the following search terms:

(carcinoma, pancreatic ductal[MeSH Terms]) AND (interleukin-6[MeSH Terms])

(carcinoma, pancreatic ductal[MeSH Terms]) AND (jak 2 protein tyrosine kinase[MeSH Terms])

(carcinoma, pancreatic ductal[MeSH Terms]) AND (jak 1 protein tyrosine kinase[MeSH Terms])

(carcinoma, pancreatic ductal[MeSH]) AND (stat3 transcription factor[MeSH Terms])

(carcinoma, pancreatic ductal[MeSH Terms]) AND (gp130, cytokine receptor[MeSH Terms])

Embase was searched using the following search query:

Fig 1. Schematic presentation of IL-6/JAK/STAT3 pathway in pancreatic cancer cells and tumor microenvironment. (PSC: pancreatic stellate cell, CAF: cancer associated fibroblast, TAM: tumor associated macrophages, MDSC: myeloid derived suppressor cells).

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Inclusion criteria were defined as all trials studying the pharmacological targeting of the GP130-related cytokine/JAK/STAT3 pathway in pancreatic cancer, including studies on animal models or cell cultures. Only studies with an English abstract were included. Reviews, comments, and conference or meeting abstracts were excluded from the analysis. No restrictions on publication date or publication status were imposed.

After exclusion of duplicates, records identified from the literature search were screened for eligibility independently by the two main authors using the title and abstract in an unblinded manner. Disagreements between the reviewers were resolved by consensus. The full-text of articles meeting the inclusion criteria was assessed by the two main authors and reevaluated for the inclusion criteria. Disagreements were, again, resolved by consensus.

We extracted data using a previously prepared extraction form. The information from each included study on the study design, characteristics of analyzed subjects or trial participants, characteristics of the pharmacological agent studied, type of outcome measures, and outcomes was tabulated. On this basis, we performed a qualitative data synthesis.

We performed a quality assessment of clinical trials according to the ROB tool, which was adapted to match non-randomized clinical trials [25]. For preclinical studies, we used the SYRCLE’s risk of bias tool, which was adapted to match in vivo and in vitro studies [26]. Results were displayed in an analogous fashion as suggested by Higgins et al for systematic reviews of interventions [25]. Bias assessment was conducted for every study by two independent assessors and disagreements resolved by consensus.

Due to the nature of this study, approval from the local Ethics Committee was not required.

Results

Study selection

Our search identified 756 records through the database searches (Embase, Pubmed) and the manual search of the reference lists of relevant articles. Initial screening excluded 689 records, including 145 duplicates. The remaining 67 articles were assessed based on the full text, 29 of which were found to be ineligible due to absence of a tested pharmacological substance or the absence of GP130-related cytokine/JAK/STAT3 pathway targeting.

A summary of the study selection process is provided in Fig 2. Ultimately, 38 studies were included in the review, including 4 ongoing trials. All included studies were published in English and no unpublished data were included. No other studies were identified through the electronic search update on October 4, 2020.
Bias assessment

Table 1 shows the risk of bias assessment for the preclinical studies. Preclinical studies had strong limitations to rigorous bias assessment because few provided sufficient details regarding selection and performance bias. Study protocols were not published beforehand, so a comparison between intended interventions and published interventions was not possible. In animal trials, few studies explicitly stated a randomization process for treatment groups, and treatment results were often assessed manually with semi-quantitative methods. This lack of reporting makes it difficult to accurately determine the risk of bias of the preclinical studies. However, more details were available on the risk of attrition bias, reporting bias, and other bias.

The quality assessment of the included clinical trials is provided in Table 2. The overall quality of the studies was good, with only one study presenting high risk of selection bias.

Preclinical studies

As summarized in Table 3, 25 of the included studies were preclinical trials testing 20 substances targeting the GP130/JAK/STAT3-pathway. Twenty-four studies performed in vitro experiments using human pancreatic cancer cells [17, 27–32, 34–36, 38–41, 43–47, 49, 50, 60, 61]. In vivo experiments were performed in 17 studies using mouse xenograft tumor models (n = 14) [28, 31, 34, 35, 38, 40–42, 44, 45, 48–50, 60], chicken chorio-allantoic membrane xenograft tumor models (n = 1) [32], or KPC mice (n = 2) [33, 45]. All studies reported favorable outcomes in terms of pancreatic cancer cell viability, proliferation, migration, colony formation ability, apoptosis, or effects on downstream target genes, as well as tumor growth, tumor volume, or weight in in vivo models. Eight studies analyzed the combinational effect of the investigated drug with chemotherapy (i.e., gemcitabine, paclitaxel, 5-fluorouracil, and oxaliplatin) [31, 33, 38, 40, 41, 45, 49, 60]. In all studies, the inhibitory effect on pancreatic cancer cells by the investigated drug was enhanced by chemotherapy.
| Reference | 1) Selection | 2) Performance | 3) Detection | 4) Reporting | 5) Other |
|-----------|--------------|----------------|--------------|--------------|----------|
| Chen 2019 | T            | B              | T            | B            | T        |
| Eu 2018   | B            | B              | B            | B            | B        |
| Ge 2015   | T            | B              | T            | B            | B        |
| Goumas 2015 | T          | T              | T            | B            | T        |
| Lin 2010 | O            | O              | T            | B            | O        |
| Long 2017 | T            | T              | T            | B            | T        |
| Palagani 2014 | T      | T              | T            | B            | T        |
| Salue 2017 | T            | T              | T            | B            | T        |
| Theoennsen 2009 | T     | T              | T            | B            | T        |
| Wu 2016 | O            | O              | O            | O            | O        |
| Zhang 2018 | T            | T              | T            | B            | T        |
| Nagaraju 2016 | T       | T              | T            | B            | T        |
| Nagaraju 2019 | T          | T              | T            | B            | T        |
| Chen 2016 | T            | T              | T            | B            | T        |
| Lin 2011 | O            | O              | O            | O            | O        |
| Heung 2016 | T            | T              | T            | B            | T        |
| Luo 2019 | T            | T              | T            | B            | T        |
| Kim 2016 | T            | T              | T            | B            | T        |
| Venkataraman 2005 | T    | T              | T            | B            | T        |
| Lu 2017 | T            | T              | T            | B            | T        |
| Liu 2019 | O            | O              | O            | O            | O        |
| Kim 2016 | T            | T              | T            | B            | T        |
| Venkatasubbara 2005 | T    | T              | T            | B            | T        |

1) Was the allocation sequence adequately generated, applied, and concealed? Were the groups similar at baseline or were they adjusted for confounders?
2) Were the caregivers and/or investigators blinded from knowledge of which intervention each animal received during the experiment?
3) Were animals/cell cultures selected at random for outcome assessment? Was the outcome assessor blinded? Was a computed/automatic tool used?
4) Are reports of the study free of selective outcome reporting?
5) Was the study apparently free of other problems that could result in high risk of bias?

V: In vivo study T: in vitro study B: in vivo and in vitro
O Meets criteria (low risk of bias) // Some concerns (unclear risk of bias, insufficient reporting) X Does not meet criteria (high risk of bias)

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As summarized in Table 4, nine of the studies were clinical trials including 880 individuals and assessing 5 drugs. One study performed a retrospective analysis of bazedoxifene, an inhibitor of the IL-6/IL-6R/GP130 complex, in patients with pancreatic (n = 5) or gastric adenocarcinoma (n = 2), showing biological tumor marker reduction in 80% and disease regression on PET-CT in 60% of cases [51]. Icatinib, a selective JAK1 inhibitor, was tested in combination with nab-paclitaxel and gemcitabine, showing a synergistic effect with an overall response rate of 24% with an acceptable safety profile in a phase 1b/2 study [52]. However, this study was terminated early due to negative phase 3 results for JAK1/2 inhibitor ruxolitinib [55]. Momelotinib, a JAK1/2 inhibitor, resulted in a partial response in 28% of patients with previously untreated metastatic PDAC (n = 25) in a phase 1 study. However, no significant difference was reported from treatment with paclitaxel and gemcitabine [53]. Ruxolitinib, a JAK1/2 inhibitor, has been investigated in phase 1b, 2, and 3 clinical trials in combination with capecitabine, gemcitabine, and paclitaxel, revealing no significant difference in overall survival or progression-free survival in patients with PDAC [54–56]. Finally, phase 2 and 3 studies have been performed assessing tipifarnib, an inhibitor of STAT3 phosphorylation that showed no single-agent antitumor activity and no difference in overall survival in combination with gemcitabine.

Table 2. Bias assessment of the clinical studies.

| Reference | Burkhardt 2019 | Beatty 2019 | Ng 2019 | Bauer 2018 | Hurwitz 2018 | Hurwitz 2015 | Eckhardt 2009 | Macdonald 2005 | Cohen 2003 |
|-----------|----------------|-------------|---------|------------|--------------|--------------|--------------|---------------|------------|
| Design Phase | R | P | P | P | P | P | P | P | P |
| 1) Selection process | X | // | // | // | O | O | O | O | O |
| 2) Deviation from intended intervention | O | O | O | O | O | O | O | O | O |
| 3) Missing outcome data | O | O | O | O | O | O | O | O | O |
| 4) Measurement of the outcome | // | O | O | O | O | O | O | O | O |
| 5) Selection of the reported result | O | O | O | O | O | O | O | O | O |
| 6) Overall | // | O | O | O | O | O | O | O | O |

1) Does the patient(s) represent(s) the whole experience of the investigator? Is the selection method clear? Was the allocation sequence random?
2) Did the investigator deviate from intended interventions? Were investigators/study participants blinded?
3) Is there evidence that the result was not biased by missing outcome data? Were incomplete outcome data adequately addressed?
4) Was the method of measuring the outcome (in)appropriate? Could measurement or ascertainment of the outcome have differed between intervention groups?
5) Were the data that produced this result analyzed in accordance with a pre-specified analysis plan?
6) Was the study apparently free of other problems that could result in high risk of bias?

R: retrospective P: prospective
O Meets criteria (low risk of bias) // Some concerns (unclear risk of bias, insufficient reporting) X Does not meet criteria (high risk of bias)

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Clinical studies

As summarized in Table 4, nine of the studies were clinical trials including 880 individuals and assessing 5 drugs. One study performed a retrospective analysis of bazedoxifene, an inhibitor of the IL-6/IL-6R/GP130 complex, in patients with pancreatic (n = 5) or gastric adenocarcinoma (n = 2), showing biological tumor marker reduction in 80% and disease regression on PET-CT in 60% of cases [51]. Icatinib, a selective JAK1 inhibitor, was tested in combination with nab-paclitaxel and gemcitabine, showing a synergistic effect with an overall response rate of 24% with an acceptable safety profile in a phase 1b/2 study [52]. However, this study was terminated early due to negative phase 3 results for JAK1/2 inhibitor ruxolitinib [55]. Momelotinib, a JAK1/2 inhibitor, resulted in a partial response in 28% of patients with previously untreated metastatic PDAC (n = 25) in a phase 1 study. However, no significant difference was reported from treatment with paclitaxel and gemcitabine [53]. Ruxolitinib, a JAK1/2 inhibitor, has been investigated in phase 1b, 2, and 3 clinical trials in combination with capecitabine, gemcitabine, and paclitaxel, revealing no significant difference in overall survival or progression-free survival in patients with PDAC [54–56]. Finally, phase 2 and 3 studies have been performed assessing tipifarnib, an inhibitor of STAT3 phosphorylation that showed no single-agent antitumor activity and no difference in overall survival in combination with gemcitabine.
Table 3. Characteristics of the included preclinical studies.

| Reference     | Study design | Drug                                | Mechanism of action                                | Subject | Number | Outcome                                                                 |
|---------------|--------------|-------------------------------------|----------------------------------------------------|---------|--------|--------------------------------------------------------------------------|
| Zhang 2018    | In vitro     | AG490 (Tyrphostin B12)             | JAK2/STAT3 inhibition                              | HPCC    | -      | ↓ cell viability, ↓ STAT3 overexpression and phosphorylation, downregulation of target genes |
| Palagani 2014 | In vitro     | AG490                               | JAK2/STAT3 inhibition                              | HPCC    | -      | In vitro: ↑ cell proliferation, ↓ apoptosis                              |
|               | In vivo      | + GSI IX + Notch (Hes1) inhibition  |                                                    | Mouse XTM | 20     | In vivo: ↓ cell proliferation, ↓ tumor growth                             |
| Wu 2016       | In vitro     | Bazedoxifene                         | Inhibitor of IL-6/IL-6R/GP130 complex              | HPCC    | -      | In vitro: ↓ STAT3 phosphorylation, downregulation of target genes, ↓ cell migration |
|               | In vivo      | + Pac + Gem                          |                                                    | Mouse XTM | 8      | In vivo: ↓ tumor growth, enhanced effect with Pac                         |
|               |              |                                      |                                                    |                      |        | No significant toxicity                                                  |
| Fu 2018       | In vitro     | Bazedoxifene + reparixin + SCH527123| Inhibitor of IL-6/IL-6R/GP130 complex              | HPCC    | -      | ↓ cell viability, ↓ cell migration, ↓ colony formation Enhanced effect with combinational therapy |
| Chen 2019     | In vitro     | Bazedoxifene                         | Inhibitor of IL-6/IL-6R/GP130 complex              | HPCC    | -      | ↓ cell viability, ↓ cell proliferation, ↓ colony formation               |
| Ge 2015       | In vitro     | Cryptotanshinone                     | STAT3 inhibition                                    | HPCC    | -      | ↑ apoptosis, downregulation of target genes                                |
| Thoennissen 2009 | In vitro      | Cucurbitacin B                       | Inhibition of phosphorylation of JAK2 and STAT3    | HPCC    | -      | In vitro: ↓ cell proliferation, ↓ apoptosis, enhanced effect with combinational therapy |
|               | In vivo      | + Gem                               |                                                    | Mouse XTM | 5      | In vivo: ↓ tumor volume, ↓ tumor weight                                 |
| Sun 2009      | In vitro     | Cucurbitacin E                       | Inhibition of STAT3 phosphorylation                 | HPCC    | -      | ↓ cell proliferation, ↑ apoptosis                                        |
| Edderkouï 2013| In vitro     | Ellagic acid                         | 1) Inhibition of STAT3 phosphorylation              | HPCC    | -      | ↓ cell proliferation, ↑ apoptosis by embelin                              |
|               | In vivo      | Embelin                              | 2) inhibition of NF-kB                              | HPCC    | -      | Enhanced effect with combinational therapy                               |
| Lin 2010      | In vitro     | FLLL31                               | Selective inhibition of JAK2/STAT3(SH2)            | HPCC    | -      | In vitro: ↓ STAT3 phosphorylation, downregulation of target genes, ↑ apoptosis |
|               | In vivo      | FLLL 32                              |                                                    | Chorio-allaotnic membrane XTM | -      | In vivo: ↓ tumor volume, ↓ neo-angiogenesis                              |
| Nagaraju 2016 | In vitro     | Ganetisib + Gem/Pac + 5-FU/Ox        | HSP90 und JAK2 inhibition                           | HPCC    | -      | In vitro: ↓ cell proliferation                                           |
|               | In vivo      |                                      |                                                    | Mouse XTM | 35     | In vivo: ↓ tumor growth, enhanced effect with combinational therapy       |
| Nagaraju 2019 | In vitro     | Ganetisib + 5-FU                     | HSP90 und JAK2 inhibition                           | HPCC    | -      | In vitro: ↓ cell proliferation, ↓ VEGF                                   |
|               | In vivo      |                                      |                                                    | Mouse XTM | 16     | In vivo: enhanced effect with combinational therapy, no significant toxicity |
| Lu 2019       | In vitro     | IL-9 antibody                        | Inhibition of IL-9                                  | HPCC    | -      | In vitro: ↓ STAT3 phosphorylation, ↓ VEGF                                 |
|               | In vivo      |                                      |                                                    | Mouse XTM | 48     | In vivo: ↓ tumor weight, ↓ survival                                      |
| Chen 2016     | In vitro     | Interleukin 32a                      | Inhibition of JAK2/STAT3                            | HPCC    | -      | Downregulation of target genes                                           |
| Liu 2011      | In vitro     | LLL12                                | Blocking of IL-6-induced STAT3 phosphorylation      | HPCC    | -      | ↓ STAT3 phosphorylation, ↓ cell viability                                |
| Huang 2016    | In vitro     | LTP-1                                | STAT3 inhibitor                                     | HPCC    | -      | In vitro: ↓ cell proliferation, ↓ cell viability, ↓ apoptosis            |
|               | In vivo      |                                      |                                                    | Mouse XTM | 40     | In vivo: ↓ tumor growth                                                  |
| Kim 2016      | In vitro     | Morusin                              | STAT3 inhibitor                                     | HPCC    | -      | ↓ STAT3 phosphorylation, downregulation of target genes, ↓ apoptosis     |

(Continued)
Four ongoing clinical trials were found, involving tocilizumab, an anti-IL6Rα antibody with favorable results in preclinical studies [31, 33], and napabucasin, a STAT3 inhibitor that is also under investigation in colorectal cancer [63].

**Discussion**

The present systematic review of 25 preclinical studies and 9 clinical trials revealed a good overall effect of the investigated drugs targeting the GP130/JAK/STAT3 pathway in the treatment of PDAC. Table 5 summarizes the outcome and the state of research for each assessed drug. Favorable outcomes have been reported for all 20 drugs investigated in a preclinical setting. Even though these substances appear promising in the treatment of PDAC, only five of these drugs have been investigated in clinical trials. Favorable outcomes and acceptable toxicity profiles have been found in studies investigating bazedoxifene and itacitinib [51, 52]. Notably,
bazedoxifene is already approved for the treatment of osteoporosis [64], and itacitinib has been shown to have great potential in recent clinical trials studying the treatment of connective tissue diseases and graft-versus-host disease, among others [65–67].

Even though the PDAC tumor micro-environment (TME) has been shown to be a promising target for improving PDAC treatment, none of the included studies in this systematic review examined the influence of the analyzed substances on stromal or immune cells.

Table 4. Characteristics of included clinical studies.

| Reference | Study design | Drug | Mechanism of action | Subject | Number | Outcome |
|-----------|--------------|------|---------------------|---------|--------|---------|
| Burkhardt 2019 [51] | Retrospective | Bazedoxifene | Inhibitor of IL-6/IL-6R/GP130 complex | PDAC | 5 | Tumor marker reduction of 80% |
| | | | | Gastric adenocarcinoma | 2 | Stability of disease on CT in 60% |
| | | | | | | Regression on PET-CT in 60% |
| Beatty 2019 [52] | Phase 1b/2 dose-finding study | Itacitinib | Selective JAK1-inhibition | Advanced PDAC | 46 | Terminated early due to futility of JANUS study [55] |
| | | | + paclitaxel | | | |
| | | | + gemcitabine | | | |
| Ng 2019 [53] | Phase 1 dose-escalation study | Momelotinib | JAK1/2 inhibitor | Untreated metastatic PDAC | 25 | No significant increase in PFS or OS |
| | | | + paclitaxel | | | |
| | | | + gemcitabine | | | |
| | | | | | | MTD: not reached |
| | | | | | | AE: fatigue (80%), nausea (76%), anemia (68%), |
| | | | | | | Partial response in 28%, stable disease in 52% |
| Hurwitz 2015 [56] | Randomized Phase 2 | Ruxolitinib | JAK1/2 inhibitor | Metastatic PDAC after treatment failure with gemcitabine | 127 | No significant increase in PFS |
| | | | + capecitabine | | | |
| | | | | | | Significant increase in OS in patients with inflammation compared to placebo (p = 0.011) |
| | | | | | | Grade 3 anemia more frequent compared to placebo |
| Bauer 2018 [54] | Phase 1b dose-finding study | Ruxolitinib | JAK1/2 inhibitor | Untreated advanced PDAC | 34 | Terminated early due to disease progression in 81% |
| | | | | | | Overall response rate in PDAC: 23.5% |
| | | | + paclitaxel | | | |
| | | | + gemcitabine | | | |
| Hurwitz 2018 [55] | Randomized Phase 3 (JANUS) | Ruxolitinib | JAK1/2 inhibitor | Advanced PDAC | 307 | Terminated early due to futility |
| | | | + capecitabine | | | |
| Eckhardt 2009 [57] | Randomized Phase 3 | Tipifarnib (R115777) | Inhibition of STAT3 phosphorylation | Advanced PDAC | 244 | No significant difference in survival |
| | | | + gemcitabine | | | |
| Macdonald 2005 [58] | Randomized Phase 2 | Tipifarnib (R115777) | Inhibition of STAT3 phosphorylation | Untreated advanced PDAC | 53 | 6-month survival rate: 19% |
| | | | | | | Median time to treatment failure: 1.4 months |
| | | | | | | No single-agent antitumor activity |
| Cohen 2003 [59] | Randomized Phase 2 | Tipifarnib (R115777) | Inhibition of STAT3 phosphorylation | Untreated advanced PDAC | 20 | 100% progression at 6 months |
| | | | | | | 6-month survival rate: 25% |
| | | | | | | No single-agent antitumor activity |

PFS: progression-free survival, OS: overall survival, MTD: maximum tolerable dose, AE: adverse event, PDAC: pancreatic ductal adenocarcinoma,— indicates no data available

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Table 5. Summary of findings by drug.

| Drug                        | Mechanism of action                     | Outcome                                      | State of research                  |
|-----------------------------|-----------------------------------------|----------------------------------------------|------------------------------------|
| Bazedoxifene                | Inhibitor of IL-6/IL-6R/GP130 complex   | Positive                                     | Clinical study, retrospective      |
|                             |                                         | Synergism with paclitaxel and gemcitabine    |                                    |
| Ganetesib                   | HSP90/JAK2                              | Positive                                     | Preclinical research               |
|                             |                                         | Synergism with gemcitabine/paclitaxel and    |                                    |
|                             |                                         | 5-fluorouracil/oxaliplatin                   |                                    |
| Ruxolitinib                 | JAK1/2 inhibitor                        | Negative in combination with gemcitabine/paclitaxel | Phase 1b clinical trial           |
|                             |                                         | Negative in combination with capecitabine    | Phase 2+3 clinical trial          |
| Tipifarnib (R1115777)       | Inhibition of STAT3 phosphorylation     | Negative as single agent                     | Phase 2 clinical trials           |
|                             |                                         | Negative in combination with gemcitabine    | Phase 3 clinical trial            |
| Momelotinib                 | JAK1/2 inhibitor                        | Negative                                     | Phase 1 clinical trial            |
|                             |                                         | Negative in combination with gemcitabine and paclitaxel |                                    |
| Itacitinib                  | Selective JAK-1 inhibition              | Positive                                     | Phase 2 clinical trial            |
| AG490                       | JAK2 inhibitor                          | Positive                                     | Preclinical research               |
| Cryptotanshinone            | STAT3 inhibition                        | Positive                                     | Preclinical research               |
| Cucurbitacin B              | Inhibition of phosphorylation of JAK2 and STAT3 | Positive; synergism with gemcitabine | Preclinical research               |
| Cucurbitacin E              | Inhibition of STAT3 phosphorylation     | Positive                                     | Preclinical research               |
| Ellagic acid                | Inhibition of STAT3 phosphorylation     | Positive                                     | Preclinical research               |
| FLLL31/32                   | Selective JAK2/STAT3 (SH2) inhibition   | Positive                                     | Preclinical research               |
| IL-32α                      | Inhibition of JAK2/STAT3                | Positive                                     | Preclinical research               |
| IL-9 antibody               | IL-9 inhibition                         | Positive                                     | Preclinical research               |
| LLL12                       | Blocking of IL-6-induced STAT3 phosphorylation | Positive               | Preclinical research               |
| LTP-1                       | STAT3 inhibitor                         | Positive                                     | Preclinical research               |
| Morusin                     | STAT3 inhibitor                         | Positive                                     | Preclinical research               |
| Phospho-valproic acid       | STAT3 inhibitor                         | Positive; synergism with gemcitabine         | Preclinical research               |
| (MDC-1112)                  |                                         |                                             |                                    |
| Ponatinib                   | Multi-receptor tyrosine kinase inhibitor | Positive                                     | Preclinical research               |
| S-Adenosylmethionine (SAM)  | Inhibition of JAK2/STAT3                | Positive; synergism with gemcitabine         | Preclinical research               |
|                             |                                         |                                             |                                    |
| SZC015                      | Suppression of NFκB and JAK2/STAT3      | Positive                                     | Preclinical research               |
| Tocilizumab                 | Anti-IL6Rα, humanized monoclonal antibody | Positive; synergism with gemcitabine       | Preclinical research               |
|                             |                                         |                                             | Ongoing clinical trials (NCT04258130, NCT02767557) |
| Napabucasin                 | STAT3 inhibitor                         | Ongoing                                      | Ongoing phase 1 and 3 clinical trials (NCT02231723, NCT02993731) |

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The TME plays an important role in tumorigenesis and chemoresistance by close interaction with tumor cells. Furthermore, TME has been shown to be highly immunosuppressive, promoting immune evasion, hence sustaining tumor progression [18–20]. Immunotherapy, so far, has not demonstrated substantial clinical improvement as single agent in the treatment of PDAC [5]. Therefore, strategies simultaneously targeting PDAC tumor cells as well as different immune checkpoints might be needed. The interactions of PDAC tumor cells and different cells within the TME such as CAFs, MDSCs, TAMs, are mediated through GP130/JAK/STAT3 pathway [11, 17–20, 68]. STAT3 inhibition might thus have consequences in shaping TME towards anti-tumor phenotype by acting on both immune and tumor cells [18–20]. In combination with chemotherapeutic agents and immunotherapy, it might significantly increase therapeutic efficacy in the treatment of PDAC.

Recent studies have shown the important role of the STAT3 pathway in tumorigenesis, as well as the STAT3-mediated resistance to chemotherapy in in vivo models of PDAC [8–15]. The results from the preclinical trials presented in this review confirmed the importance of the GP130/JAK/STAT3 pathway in PDAC and its role as a possible drug target. Furthermore, several of the studies showed a synergy between the investigational drug and chemotherapy, such as gemcitabine, paclitaxel, 5-fluorouracil, and oxaliplatin [31, 33, 38, 40, 41, 45, 49, 53–55, 57, 60]. However, to the best of our knowledge, drugs targeting GP130/JAK/STAT3 have never been studied as chemosensitizers in addition to the currently emerging FOLFIRINOX regimen [4]. Even though some promising outcomes have been shown in clinical trials [51, 52], several studies were terminated prematurely due to high progression rates and futility. This may reflect the difficulty showing a significant benefit in patients presenting with PDAC, as it is known to be a highly lethal disease that is often diagnosed at an advanced stage and has a poor prognosis with an overall 5-year survival rate of 2–9% [1, 2].

The discrepancy between preclinical and clinical data may also result from the fact that, in contrast to the preclinical studies, the clinical trials did not verify the activation of the STAT3 pathway in PDAC. The benefit of targeted GP130/JAK/STAT3 therapy may be increased by selecting patients with previously known STAT3 pathway activation in PDAC cells.

The present systematic review included all preclinical and clinical trials of drugs targeting the GP130/JAK/STAT3 pathway. Furthermore, we searched for ongoing, unpublished trials, leading to a thorough analysis of the current state of research. However, because all published preclinical studies reported a positive outcome, we suspect that several negative studies may not have been published and concluded relevant publication bias, leading to an overestimation of the effect of GP130/JAK/STAT3-targeting drugs in the treatment of PDAC in the preclinical setting. Furthermore, the substantial heterogeneity among the preclinical and clinical studies did not allow a quantitative analysis or measurement of the effect size.

**Conclusion**

Preclinical studies strongly suggest significant efficacy of drugs targeting GP130/JAK/STAT3 in the treatment of PDAC and that these molecules are effective chemosensitizers, possibly through simultaneous effect on tumor cells and TME. Though only a few trials have shown the efficacy in a clinical setting, the GP130/JAK/STAT3 pathway remains a promising drug target for the development of future treatments for PDAC and may help overcome chemotherapy resistance.

**Supporting information**

S1 Checklist.

(DOC)
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