

STAT3 Inhibitors for Cancer Therapy –the Rationale and Remained Problems

Tomohiro Chiba

Department of Pathology, Kyorin University School of Medicine, Japan

***Corresponding Author:** Tomohiro Chiba, Department of Pathology, Kyorin University School of Medicine, Japan.

Received: January 08, 2016; **Published:** January 08, 2016

Abstract

STAT3 regulates various cellular functions, which is diverted to malignant phenotypes of cancer cells. Aberrant activation of STAT3 in cancer cells has motivated researchers to develop STAT3 inhibitors as a novel line of anti-cancer drugs. The attempt has not been successful so far. There are some hurdles to be overcome. Basic concepts of STAT3 inhibitors and remained problems will be discussed.

Keywords: STAT3; Cancer; Therapy; Tyrosine Kinase; Signal Transduction

Abbreviations: CC domain: Coiled Coil domain; CCND1: Cyclin D1; DBD domain: DNA-Binding domain; EGFR: Epidermal Growth Factor Receptor; ER: Estrogen Receptor; FLT3: Fms-Like Tyrosine kinase 3; FDA: U.S. Food and Drug Administration; HR: Hazard Ratio; IL-6: Interleukin 6; JAK: Janus kinase; miR: microRNA; MF: Myelofibrosis; NSCLC: Non-Small-Cell Lung Cancer; OS: Overall Survival; PTEN: Phosphatase and Tensin Homolog; PRC2: Polycomb Repressive Complex 2; PD1: Programmed Cell Death 1; PD-L1: Programmed Death-Ligand 1; PIAS3: Protein Inhibitor of Activated STAT3; PTP: Protein Tyrosine Phosphatase; RFS: Relapse-Free Survival; STAT3: Signal Transducer and Activator of Transcription 3; SH2 domain: Src Homology 2 domain; SOCS3: Suppressor of Cytokine Signaling-3; SLE: Systemic Lupus Erythematosus; TA domain: Transactivation Domain

STAT3 as an attractive target in cancer therapy –the rationale for STAT3 inhibitors

STAT3 is originally identified as an intracellular signal transducing protein activated by cytokines such as IL-6 [1,2]. Uniquely, STAT3 homodimerizes upon activation by phosphorylation at Tyr 705 (Y705), and is translocated to the nucleus, regulating gene expression as a transcription factor (Figure 1a-c). There are several target genes of STAT3, including cell cycle regulators such as CCND1 and p21^{WAF/CIP1}, proto-oncogene such as *c-Myc* and *c-Fos*, and also anti-apoptotic genes such as *Bcl-2* and *Bcl-xL* [3]. Together with the fact that STAT3 is phosphorylated by upstream tyrosine kinases such as JAKs (JAK1, JAK2, JAK3 and TYK2), EGFR, HER2 and Src, STAT3 is regarded as a key cellular-signalling molecule in the proliferation and survival of cancer cells. Consistently, survival of many cancer cell lines essentially depends on STAT3 activation, which is called as “STAT3 addiction” phenotype.

STAT3 activation is also involved in malignant phenotypes of cancer cells. Cancer stem cell phenotypes, facilitating drug resistance and tumor recurrence, are maintained by STAT3 activation, at least, in glioblastoma and breast cancer [4]. Epithelial-mesenchymal transition (EMT), which launches tumor metastasis, requires STAT3 activation in multiple lines of cancer cells [5]. In accordance, STAT3 transcriptionally regulates stemness-related genes such as *c-Myc*, *Sox2* and *Nanog*, and also EMT-related genes such as *Twist1*, *ZEB1* and *MMP2* [3]. Several lines of *in vitro* and *in vivo* experimental evidence in contrast support the notion that STAT3 inhibition suppresses cancer exacerbation.

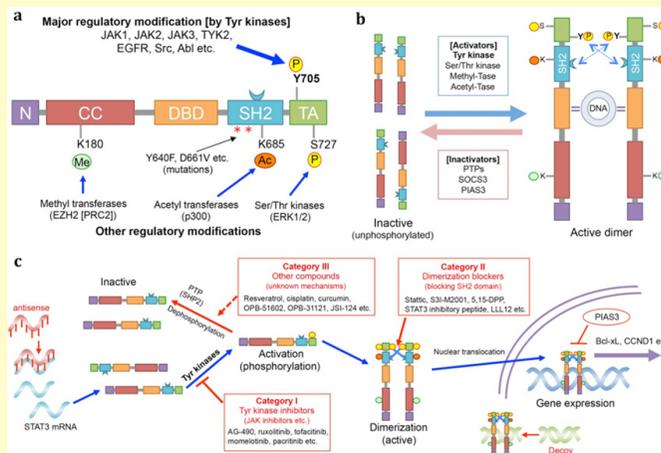


Figure 1: Schematic summary of STAT3 inhibitors in relation to STAT3 structure.

- a. Structure of STAT3 and its post-translational modifications. STAT3 is consisting of N-terminal domain (N), coiled-coil domain (CC), DNA-binding domain (DBD), SH2 domain and transactivation domain (TA). STAT3 is activated by phosphorylation of Y705. Other types of post-translational modifications including K180 methylation, K685 acetylation and S727 phosphorylation are also involved in STAT3 activation.
- b. STAT3 homodimerizes using the phospho-Y705 and SH2 domain. Inactive or unphosphorylated STAT3 might be monomers or loose dimers. SOCS3, PTPs and PIAS3 are endogenous negative regulators of STAT3.
- c. STAT3 inhibitors can be classified into three categories: Category I) inhibitors of upstream Tyr kinases such as JAKs, Category II) dimerization blockers targeting SH2 domain and Category III) miscellaneous compounds inducing STAT3 dephosphorylation.

Another noteworthy aspect of STAT3 is the critical involvement in the tumor microenvironment. As cytokines are regulators of inflammation, STAT3 is reported to regulate immune system against cancer. Cancer-supporting M2 type macrophages are induced by the activation of IL-6/STAT3 pathway [6]. STAT3 is also reported to upregulate CTLA-4, PD-1 and PD-L1, which is involved in immune checkpoint regulation to induce antitumor immune responses [7-9]. In addition to the immune system, cancer-associated fibroblasts [10] and tumor angiogenesis [11] are also regulated by STAT3 activation.

STAT3 is not only aberrantly over expressed, but also correlated with poor prognosis in several malignancies including breast cancer, lung cancer, gastric cancer, pancreatic cancer, ovarian cancer, leukemia, lymphomas, melanoma and brain tumors [1-3]. Based on the bioinformatics analyses using public databases (Kaplan-Meier Plotter: <http://kmplot.com/analysis/>), it is confirmed that STAT3 over expression is significantly linked to poor prognosis in breast cancer, NSCLC (adenocarcinoma) and gastric cancers as shown in Figure 2a-d [12,13]. In addition, somatic gain-of function mutations in STAT3 gene (Y640F, D661V etc., located in the SH2 domain) were finally identified in large granular lymphocytic leukemia and other T-cell lymphomas (Figure 1a) [14,15]. STAT3 is, thus, attracting many researchers’ attention as a novel target for anti-cancer drugs.

How to inhibit STAT3?

STAT3 function requires Tyr phosphorylation, homodimerization using an SH2 domain and phosphorylated-Tyr at 705, and binding to target DNA sequences Figure 1c. STAT3 is phosphorylated by upstream JAK tyrosine kinases, and is inactivated by endogenous molecules such as SOCS3, SHP2 and PIAS3 (Figure 1b and 1c). Expression of SOCS3 is induced by activated STAT3 and SOCS3 inhibits JAK to suppress STAT3 activation in a negative feedback fashion [1,2]. PTPs like SHP2 dephosphorylate STAT3 [16]. PIAS3, a nuclear protein with SMO E3 Ligase activity, inactivates STAT3 via multiple mechanisms [17].

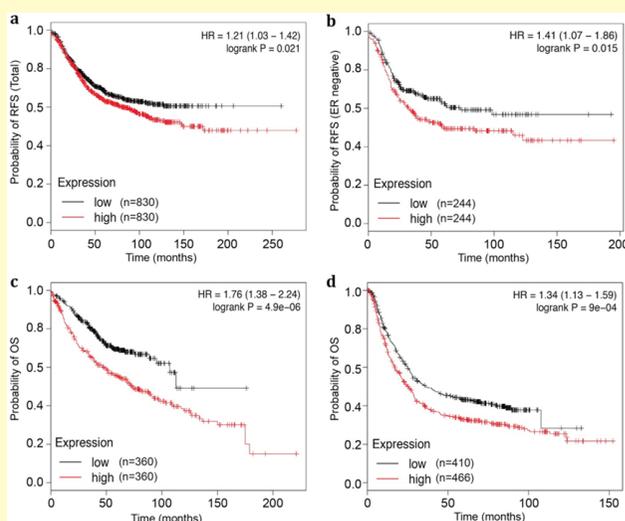


Figure 2: Poor prognosis in cancer patients with high STAT3 expression. Kaplan-Meier curves are drawn for patients with high and low STAT3 expression levels using public microarray data (Affymetrix ID: 225289_at [STAT3]) by Kaplan-Meier Plotter online software (<http://kmplot.com/analysis/>). Hazard ratios (HR) and p-values of log rank test are indicated in each panel.

a. Probability of relapse-free survival (RFS) of breast cancer patients (Total).

b. Probability of RFS of breast cancer patients (ER negative).

c. Probability of overall survival (OS) of lung adenocarcinoma patients.

d. Probability of OS of gastric cancer patients.

There are three major classes of STAT3 inhibitors (Figure 1c) [18,19]: i) upstream Tyr kinase inhibitors such as JAK inhibitors (AG-490, ruxolitinib, tofacitinib, lestaurtinib, momelotinib, baricitinib, pacritinib, fedratinib etc.), ii) STAT3 dimerization blockers targeting the SH2 domain such as Static, S3I-M2001, STAT3 inhibitory peptide, 5,15-DPP, rPP-C8, LLL12, FLLL31 and FLLL32, and iii) miscellaneous compounds inducing STAT3 dephosphorylation such as resveratrol, cisplatin, OPB-51602, OPB-31121, curcumin, cucurbitacins (JSI-124 etc.) and nifroxazide. Some Tyr kinase inhibitors are specific for a certain upstream kinase such as JAK2 specific inhibitors, AG-490, Fedratinib and AZD1480. Other Tyr kinase inhibitors elicit rather broad spectrum of kinase inhibition resulting in suppression of multiple signalling pathways besides the STAT3 pathway. Especially in cancer cells, Tyr kinases such as Src and Abl also phosphorylate STAT3. Dimerization blockers, in general, need relatively high concentration such as low micromolar concentrations to suppress STAT3 activity. Natural compounds like resveratrol and curcumin are reported to suppress STAT3 via indirect mechanisms. These compounds are not specific and also inhibit other signalling pathway such as the NF- κ B pathway.

In addition to the inhibitors above, novel types of STAT3 inhibitors are under development, which could be based on activation of endogenous STAT3-suppressing molecules such as SOCS3, SHP2 and PIAS3. Nucleic acid-based inhibitors such as an antisense oligonucleotides (AZD9150), a G-quartet-based inhibitor (GQ-ODNGQ-ODN), and a double-stranded STAT3 decoy DNA are also designed to inhibit STAT3 transcription or STAT3 binding to target DNA sequences. miRs targeting STAT3 or regulators of STAT3 pathway are also interesting candidates for STAT3 inhibitors.

STAT3 inhibitors on the way

Several pharmaceutical companies and researchers are currently trying to develop STAT3 inhibiting reagents. Most of them are upstream JAK inhibitors presumably because the rationale of JAK inhibition is solid, i.e. a constitutive active mutation of JAK2 (JAK2_{V617F}) is frequently found in myeloproliferative disorders [20]. Two JAK inhibitors are currently approved for myelofibrosis (MF) by the FDA.

Ruxolitinib (INCB018424), an oral JAK1/2 inhibitor, showed marked clinical benefits for patients with MF in Phase II (NCT00509899 and NCT00952289 [COMFORT-I]) [21,22] and Phase III studies (NCT00934544 [COMFORT-II]) [23]. FDA approved ruxolitinib for MF in 2011. IL-6/JAK1/STAT3 pathway is also implicated in the inflammatory disorders including rheumatoid arthritis (RA) and psoriasis. A Phase III study of an oral JAK inhibitor (especially JAK3 and JAK1), tofacitinib (CP-690,550), for RA, was carried out and demonstrated clinical benefits (NCT00814307) [24]. FDA approved tofacitinib for RA in 2012.

In addition, there are several JAK inhibitors, currently tested in clinical trials, including a JAK1/2 inhibitor baricitinib (LY3009104, INCB028050) [25], a JAK1/2 inhibitor momelotinib (CYT387) (NCT00935987), a JAK2/FLT3 inhibitor pacritinib (NCT01773187 [PER-SIST-1]), a selective JAK1 inhibitor fligotinib (GLPG0634)(NCT01888874 [DARWIN1] and NCT01894516 [DARWIN2]), and a cell-permeable AG490 analogue (a JAK2 inhibitor) WP1066 (NCT01904123).

On the other hands, some JAK inhibitors have been given up due to relatively severe adverse events. A JAK2 inhibitor, fedratinib (SAR302503, TG101348), significantly improved MF in a Phase III study (NCT01437787) [26]. Unfortunately, however, Sanofi decided to discontinue clinical development of fedratinib due to neurological adverse events resembling Wernicke's encephalopathy (Nov. 18th, 2013, <http://en.sanofi.com>). A JAK1/2 inhibitor, AZD1480, also caused neurological adverse events such as dizziness, anxiety, ataxia, memory loss, hallucination and behavioral changes, leading to discontinuation of clinical development (NCT01112397) [27]. Phase II studies of lestaurtinib (CEP-701), an oral JAK2 and FLT3 inhibitor, demonstrated only modest efficacy in MF patients but evoked frequent gastrointestinal toxicity (NCT00494585) [28]. Clinical development of lestaurtinib was discontinued. GSK2586184 (GLPG0778) caused eosinophilic and systemic symptoms (DRESS) syndrome and severe liver dysfunction in a Phase II study for SLE (NCT01777256) [29]. GlaxoSmithKline halted clinical development of GSK2586184 for inflammatory disorders. Momelotinib, currently under development, also showed a neurological adverse effect, peripheral neuropathy, in up to 44% of patients [30].

Compounds suppressing STAT3 phosphorylation independently of JAK inhibition are attracting attention. A Phase I study of an oral STAT3 phosphorylation inhibitor, OPB-51602, was carried out in patients with refractory haematological (NCT01344876) and solid malignancies (NCT01184807). Some promising antitumor activity of OPB-51602 was observed in NSCLC patients. Long term administration of OPB-51602, however, seemed to be difficult due to dose-limiting toxicities including lactic acidosis [31,32]. An oral inhibitor OPB-31121, which inhibits both STAT3 and STAT5 via unknown mechanisms, was well tolerated in an initial Phase I trial (NCT00955812) [33]. In a Phase I/II study, OPB-31121, however, showed insufficient antitumor activity for patients with advanced hepatocellular carcinoma and caused unfavourable adverse events including peripheral nervous system-related toxicity (NCT01406574) [34]. A number of clinical trials using resveratrol and curcumin for malignancies are also ongoing.

Other types of STAT3 inhibitors are also underway. A Phase 0 study of STAT3 decoy oligonucleotides (NSC-741763) for head and neck cancer is reported (NCT00696176) [35]. A Phase 1/2 study of a linear antisense RNA, IONIS-STAT3Rx (AZD9150), for advanced cancers, is ongoing (NCT01563302). STAT3 dimerization blockers such as Stattic, S31-M2001 and LLL12 are, however, still preclinical.

Remained problems in STAT3 inhibition

First of all, there are no clinically approved drugs directly targeting STAT3, so far. Accordingly, some researchers regard STAT3 as an "undruggable target". Currently approved drugs are, in most cases, inhibitors of enzymes or cell surface receptors, both of which amplify cellular signalling with extremely high efficiency. Consequently, inhibition of enzymatic molecules, even if it is partial, generally results in intensive suppression of cellular signalling. On the other hand, STAT3 molecules transduce cellular signalling molecules transducers cellular are signalling by itself without amplification. Therefore complete inhibition of STAT3 signalling pathway, for example, requires total inhibition of STAT3 molecules in the cell, which could be achieved at high drug concentrations. Proteins like STAT3 are, certainly, formidable enemy of drug developers. JAKs are reasonable targets in inhibiting STAT3 pathway except that JAKs also phosphorylate a variety of substrates including other STAT family proteins, IRS-1, Shc and so on [1-3]. Development of highly efficient inhibitors directly targeting STAT3 is craved.

JAK inhibitors are successful as they have shown clinical benefits in myeloproliferative diseases such as MF and inflammatory disorders such as RA and psoriasis. Ruxolitinib and tofacitinib will be frequently used, at least for MF, in the clinics. As to STAT3 constitutively activated malignant neoplasms such as breast cancer, glioblastoma and gastric cancer, we have to wait for the results of clinical trials currently ongoing.

Another problem in STAT3 inhibition seems to be the adverse effects. As mentioned above, several inhibitors have been discontinued from clinical development due to severe adverse events. Toxicities along with systemic STAT3 inhibition are expected because STAT3 is ubiquitously expressed through the whole body and also because STAT3 disruption in mice caused early embryonic lethality at around E6.5-7.5 [36]. Actually, various adverse events are reported: e.g. fatigue, nausea, diarrhea, anemia, infection etc. It is notable that JAK inhibitors frequently cause neurological adverse events. In consistence, inactivation of STAT3 in hippocampal neurons might be involved in the pathogenesis of Alzheimer's disease [37]. Improvement of drug delivery and target specificity will reduce or alleviate adverse events related to STAT3 inhibition although it might be difficult to avoid them.

STAT3 overexpression is reported in various cancers [1-3]. Most of such studies utilize gene expression analyses based on microarrays or RNA sequencing by next-generation sequencers. STAT3 activity is, however, tightly regulated by post-translational modifications, not by the protein expression levels. It is mandatory to analyze activated STAT3 in cancer samples. In addition, STAT3 is expressed in both cancer cells and non-neoplastic normal cells surrounding cancer cells. Correlation between STAT3 activity and tumor progression thus should be carefully addressed.

Context-dependent roles of STAT3 in cell survival should be also addressed. STAT3 activation, in most cases, promotes cell survival and proliferation, especially in malignancies. It is, however, reported that STAT3 activation promotes mammary gland involution via induction of lysosome-dependent death in mammary duct epithelium [38]. TYK2/STAT3 signalling is also reported to mediate β -amyloid-induced neuronal death [39]. Moreover, STAT3 overexpression is reported to be linked to better prognosis in well-differentiated thyroid cancer [40], although the mechanisms underlying STAT3-mediated suppression of thyroid cancer progression are still enigmatic. Transient over activation of STAT3 in normal cells with low basal STAT3 activity seems to induce cell death while survival of tumor cells with moderately elevated basal STAT3 activity seems to be dependent on or "addicted" to STAT3 activation. STAT3 inhibitors, therefore, should be used in patients with STAT3 highly activated cancers after appropriate measurements of basal STAT3 activity in cancer cells.

Prospects of STAT3 inhibitors

STAT3 targeted drugs are yet to be accomplished although many JAK inhibitors, which reduce STAT3 Tyr phosphorylation, are now getting in clinical use. Novel findings about STAT3 might help with development of other types of STAT3 inhibitors. Several types of post-translational modifications, besides Y705 phosphorylation, are required for activation of STAT3 (Figure 1a). S727 phosphorylation of STAT3 by ERK1/2 induces full activation of STAT3 [41]. K685 acetylation of STAT3, mediated by a histone acetyltransferase p300, is involved in dimerization of STAT3 [42]. K180 methylation of STAT3, mediated by a lysine methyltransferase EZH2 included in the polycomb repressive complex 2 (PRC2), is also required for STAT3 activation [43]. STAT3 inhibitors other than JAK inhibitors can be developed, at least, by targeting these Ser/Thr kinases, acetyltransferase and methyltransferase. STAT3 activation could be inhibited as well by small compounds or molecules, which bind to and mask the amino acid side chains used in the STAT3 modifications.

Several microRNAs (miRs) are reported to be involved in the regulation of STAT3 activity. STAT3 mRNA is directly bound at its 3' UTR region by the miR-17 cluster (also known as OncomiR-1) family members such as miRs-17, -20a and 106b [44]. In addition, miRs let-7a, -20b and -125b are also direct suppressors of STAT3 expression. STAT3, on the other hand, directly binds to and activates the miR17-92 cluster promoter. Expression of miRs-21 and -181b is also directly up regulated by STAT3, leading to suppression of PTEN and activation of NF- κ B. The miRs can be utilized or targeted in STAT3 inhibiting therapy.

In summary, STAT3 is an attractive target in cancer therapy with compiled evidence of its critical involvement in cancer progression. JAK inhibitors are generally successful in patients with myeloproliferative disorders although relatively frequent adverse events should be noted. It seems to be much difficult, on the other hand, to develop direct STAT3 inhibitors. Distinct strategies, other than simple

Citation: Tomohiro Chiba. "STAT3 Inhibitors for Cancer Therapy –the Rationale and Remained Problems". *EC Cancer* 1.S1 (2016): S1-S8.

inhibition of STAT3 dimerization, might provide promising candidates. Solution of the above mentioned problems in STAT3 inhibition and further molecular analyses of STAT3 activation and regulation will be definitely helpful in developing novel inhibitors.

Acknowledgements

I am grateful to my mentor late Dr. Ikuo Nishimoto, who passed away on Oct. 17, 2003. I also thank Ms. Tomo Nishimoto for indispensable support. This work was supported in part by grants from the Japan Society for the Promotion of Science (JSPS KAKENHI Grant No. 25871006).

Conflict of interest

The author declares here that any financial interest or any conflict of interest exists.

Bibliography

1. Esteban R., *et al.* "Photoprotective implications of leaf variegation in *E. dens-canis* L. and *P. officinalis* L." *Journal of Plant Physiology* 165.12 (2008): 1255-1263.
2. Chiba T., *et al.* "Targeting the JAK2/STAT3 axis in Alzheimer's disease." *Expert Opinion on Therapeutic Targets* 13.10 (2009): 1155-2267.
3. Yu H., *et al.* "Revisiting STAT3 signalling in cancer: new and unexpected biological functions." *Nature Reviews Cancer* 14.11 (2014): 736-746.
4. Carpenter RL and Lo HW. "STAT3 Target Genes Relevant to Human Cancers." *Cancers* 6.2 (2014): 897-925.
5. Guryanova OA., *et al.* "Nonreceptor tyrosine kinase BMX maintains self-renewal and tumorigenic potential of glioblastoma stem cells by activating STAT3." *Cancer Cell* 19.4 (2011): 498-511.
6. Lo HW., *et al.* "Epidermal growth factor receptor cooperates with signal transducer and activator of transcription 3 to induce epithelial-mesenchymal transition in cancer cells via up-regulation of TWIST gene expression." *Cancer Research* 67.19 (2007): 9066-9076.
7. Dijkgraaf EM., *et al.* "Chemotherapy alters monocyte differentiation to favor generation of cancer-supporting M2 macrophages in the tumor microenvironment." *Cancer Research* 73.8 (2013): 2480-2492.
8. Yu CR., *et al.* "SOCS3 deletion in T lymphocytes suppresses development of chronic ocular inflammation via upregulation of CTLA-4 and expansion of regulatory T cells." *Journal of Immunology* 191.10 (2013): 5036-5043.
9. Austin JW., *et al.* "STAT3, STAT4, NFATc1, and CTCF regulate PD-1 through multiple novel regulatory regions in murine T cells." *Journal of Immunology* 192.10 (2014): 4876-4886.
10. Hossain DM., *et al.* "Leukemia cell-targeted STAT3 silencing and TLR9 triggering generate systemic antitumor immunity." *Blood* 123.1 (2014): 15-25.
11. Lee KW., *et al.* "Twist1 is a key regulator of cancer-associated fibroblasts." *Cancer Research* 75.1. (2015): 73-85.
12. Niu G., *et al.* "Constitutive Stat3 activity up-regulates VEGF expression and tumor angiogenesis." *Oncogene* 21.13 (2002): 2000-2008.
13. Györfy B., *et al.* "An online survival analysis tool to rapidly assess the effect of 22,277 genes on breast cancer prognosis using microarray data of 1809 patients." *Breast Cancer Research and Treatment* 123.3 (2010): 725-731.
14. Györfy B., *et al.* "Online survival analysis software to assess the prognostic value of biomarkers using transcriptomic data in non-small-cell lung cancer." *PLoS One* 8.12 (2013): e82241.
15. Koskela HL., *et al.* "Somatic STAT3 mutations in large granular lymphocytic leukemia." *New England Journal of Medicine* 366.20 (2012): 1905-1913.
16. Ohgami RS., *et al.* "STAT3 mutations are frequent in CD30+ T-cell lymphomas and T-cell large granular lymphocytic leukemia." *Leukemia* 27.11 (2013): 2244-2247.
17. Howlett M., *et al.* "Cytokine signalling via gp130 in gastric cancer." *Biochimica et Biophysica Acta (BBA) – Molecular Cell Research* 1793.11 (2009): 1623-1633.

Citation: Tomohiro Chiba. "STAT3 Inhibitors for Cancer Therapy –the Rationale and Remained Problems". *EC Cancer* 1.S1 (2016): S1-S8.

18. Yagil, Z., *et al.* "The enigma of the role of protein inhibitor of activated STAT3 (PIAS3) in the immune response." *Trends in Immunology* 31.5 (2010): 199-204.
19. Mankan AK and Greten FR. "Inhibiting signal transducer and activator of transcription 3: rationality and rationale design of inhibitors." *Expert Opinion on Investigational Drugs* 20.9 (2011): 1263-1275.
20. Chiba T, *et al.* "Stat3 inhibition in neural lineage cells." *Hormone Molecular Biology and Clinical Investigation* 10.2 (2012): 255-263.
21. Viny AD and Levine RL. "Genetics of myeloproliferative neoplasms." *Cancer Journal* 20.1 (2014): 61-65.
22. Verstovsek S, *et al.* "Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis." *New England Journal of Medicine* 363.12 (2010): 1117-1127.
23. Verstovsek S, *et al.* "A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis." *New England Journal of Medicine* 366.9 (2012): 799-807.
24. Cervantes F, *et al.* "Three-year efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for myelofibrosis." *Blood* 122.25 (2013): 4047-4053.
25. Fleischmann R, *et al.* "Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis." *New England Journal of Medicine* 367.6 (2012): 495-507.
26. Shi JG, *et al.* "The pharmacokinetics, pharmacodynamics, and safety of baricitinib, an oral JAK 1/2 inhibitor, in healthy volunteers." *Journal of Clinical Pharmacology* 54.12 (2014): 1354-1361.
27. Pardanani A, *et al.* "Safety and Efficacy of Fedratinib in Patients With Primary or Secondary Myelofibrosis: A Randomized Clinical Trial." *JAMA Oncology* 1.5 (2015): 643-651.
28. Plimack ER, *et al.* "AZD1480: a phase I study of a novel JAK2 inhibitor in solid tumors." *The Oncologist* 18.7 (2013): 819-820.
29. Santos FP, *et al.* "Phase 2 study of CEP-701, an orally available JAK2 inhibitor, in patients with primary or post-polycythemia vera/essential thrombocythemia/myelofibrosis." *Blood* 115.6 (2010): 1131-1136.
30. van Vollenhoven RF, *et al.* "DRESS syndrome and reversible liver function abnormalities in patients with systemic lupus erythematosus treated with the highly selective JAK-1 inhibitor GSK2586184." *Lupus* 24.6 (2015): 648-649.
31. Abdelrahman RA, *et al.* "Momelotinib treatment-emergent neuropathy: prevalence, risk factors and outcome in 100 patients with myelofibrosis." *British Journal of Haematology* 169.1 (2015): 77-80.
32. Wong AL, *et al.* "Phase I and biomarker study of OPB-51602, a novel signal transducer and activator of transcription (STAT) 3 inhibitor, in patients with refractory solid malignancies." *Annals of Oncology* 26.5 (2015): 998-1005.
33. Ogura M, *et al.* "Phase I study of OPB-51602, an oral inhibitor of signal transducer and activator of transcription 3, in patients with relapsed/refractory hematological malignancies." *Cancer Science* 106.7 (2015): 896-901.
34. Bendell JC, *et al.* "Phase 1, open-label, dose-escalation, and pharmacokinetic study of STAT3 inhibitor OPB-31121 in subjects with advanced solid tumors." *Cancer Chemotherapy and Pharmacology* 74.1 (2014): 125-130.
35. Okusaka T, *et al.* "Phase 1 and pharmacological trial of OPB-31121, a signal transducer and activator of transcription-3 inhibitor, in patients with advanced hepatocellular carcinoma." *Hepatology Research* (2015).
36. Sen M, *et al.* "First-in-human trial of a STAT3 decoy oligonucleotide in head and neck tumors: implications for cancer therapy." *Cancer Discovery* 2.8 (2012): 694-705.
37. Takeda K, *et al.* "Targeted disruption of the mouse Stat3 gene leads to early embryonic lethality." *Proceedings of the National Academy of Sciences of the United States of America* 94.8 (1997): 3801-3804.
38. Chiba T, *et al.* "Amyloid-beta causes memory impairment by disturbing the JAK2/STAT3 axis in hippocampal neurons." *Molecular Psychiatry* 14.2 (2009): 206-222.
39. Kreuzaler PA, *et al.* "Stat3 controls lysosomal-mediated cell death *in vivo*." *Nature Cell Biology* 13.3 (2011): 303-309.
40. Wan J, *et al.* "Tyk2/STAT3 signaling mediates beta-amyloid-induced neuronal cell death: implications in Alzheimer's disease." *Journal of Neuroscience* 30.20 (2010): 6873-6881.

41. Couto JP, *et al.* "STAT3 negatively regulates thyroid tumorigenesis." *Proceedings of the National Academy of Sciences of the United States of America* 109.35 (2012): E2361-E2370.
42. Plaza-Menacho I, *et al.* "Ras/ERK1/2-mediated STAT3 Ser727 phosphorylation by familial medullary thyroid carcinoma-associated RET mutants induces full activation of STAT3 and is required for c-fos promoter activation, cell mitogenicity, and transformation." *Journal of Biological Chemistry* 282.9 (2007): 6415-6424.
43. Yuan ZL, *et al.* "Stat3 dimerization regulated by reversible acetylation of a single lysine residue." *Science* 307.5707 (2005): 269-273.
44. Kim E, *et al.* "Phosphorylation of EZH2 activates STAT3 signaling via STAT3 methylation and promotes tumorigenicity of glioblastoma stem-like cells." *Cancer Cell* 23.6 (2013): 839-852.
45. Kohanbash G and Okad, H. "MicroRNAs and STAT interplay." *Seminars in Cancer Biology* 22.1 (2012): 70-75.

Volume 1 Issue S1 January 2016

© All rights are reserved by Tomohiro Chiba.