A Review on Tyrosine Kinase 2 Inhibitors for the Treatment of Cancer

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (B.Pharm.)

School of Pharmacy
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis/project titled "A Review on Tyrosine Kinase 2 Inhibitors for the Treatment of Cancer." submitted by Jannatul Ferdous Sumiya(19346048) of Summer, 19 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy

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Ethics Statement

This project is a review article and it does not involve any animal trials (pre- clinical trials) or clinical trials on human.

Abstract

Tyrosine kinase 2 (TYK2) encodes a signaling protein found in cells. TYK2 is being studied as a cancer treatment target due to its role in immune modulation and inflammation. Tyrosine kinase 2 inhibitors block tyrosine kinases, which are essential for cell proliferation, differentiation, and survival. TYK2 inhibitors have been thoroughly investigated for autoimmune diseases but recent development shows potency towards cancer treatments. This review is comprised of an updated compilation of TYK2 inhibitors that are available in the market for the treatment of cancer such as Deucravacitinib, Ruxolitinib, Fedratinib. And some are in the clinical phases such as Ropsacitinib and BMS-986202. However, the existing TYK2 inhibitors can cause resistance and adverse effects due to the. Therefore, more potent and selective inhibitors are needed to be developed. Lastly, this review discusses various approaches of discovering improved TYK2 inhibitors that can be used in the treatment of cancer.

Keywords: Tyrosine Kinase 2, Tyrosine Kinase 2 Inhibitors, Cancer, Protein Kinase, Deucravacitinib, Fedratinib.

Dedication

Dedicated to my faculty members and family.

Acknowledgement

I would like to take this opportunity to extend sincere gratitude to my project supervisor, Assistant Professor, Dr. Nishat Zareen Khair, for giving me with the direction and guidance I needed to successfully complete my project. She also took the time to proofread and fix my mistakes, and I am really grateful to her. For the chance to conduct my research, I am also grateful to our School of Pharmacy Dean, Dr. Eva Rahman Kabir, and our Assistant Dean, Dr. Hasina Yasmin.

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List of Acronyms

TKI	Tyrosine Kinase Inhibitors
JAK	Janus Kinase
PTK	Protein Tyrosine Kinase
ATP	Adenosine Triphosphate
TYK 2	Tyrosine Kinase 2
FDA	Food And Drug Administration
STAT	Signal Transducers and activators of transcription
ABI	Ankle Brachial Index
TNF	Tumor Necrosis Factor
CAD	Coronary Artery Disease
HTN	Hypertension
DM	Diabetes Mellitus
ABI	Ankle Brachial Index
MPN	Myeloproliferative Neoplasms
ECHO	Electrocardiogram
RTK	Receptor Tyrosine Kinase
NRTK	Non-Receptor Tyrosine Kinase

Chapter 1

Introduction

1.1 Overview of Protein Tyrosine Kinase

Protein tyrosine kinases (PTKs) are enzymes that catalyzes the transfer of the phosphate group of ATP to tyrosine residues of protein substrates. Hubbard et al. (1998), Hubbard and Till (2000) describe the various post translational changes and intra- and intermolecular complex forms that regulate PTK activity. PTKs have been linked to the control of several biological processes, including cell migration, proliferation, differentiation, and survival. It has been demonstrated that they impact a wide range of medical disorders, such as immunosuppression, atherosclerosis, psoriasis, osteoporosis, diabetes, and cancer. Two primary categories of protein tyrosine kinases (PTKs) exist: receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases. (Alain Enjalbert, 2003) (Thomas A. Hamilton, 1998)

1.2 Classification of Protein Kinase

The five main categories of protein kinases are based on the amino acid residues that they phosphorylate.

- Serine/threonine protein kinase,
- Tyrosine protein kinases,
- Histidine-specific protein kinases,
- Dual-specific protein kinases and
- Aspartic acid/glutamic acid specific protein kinases.

One kind of protein kinase is the tyrosine kinase, which attaches phosphate groups to different types of amino acids. (Schlegel U, 2000)

1.3 Structure of Tyrosine Kinase Receptor

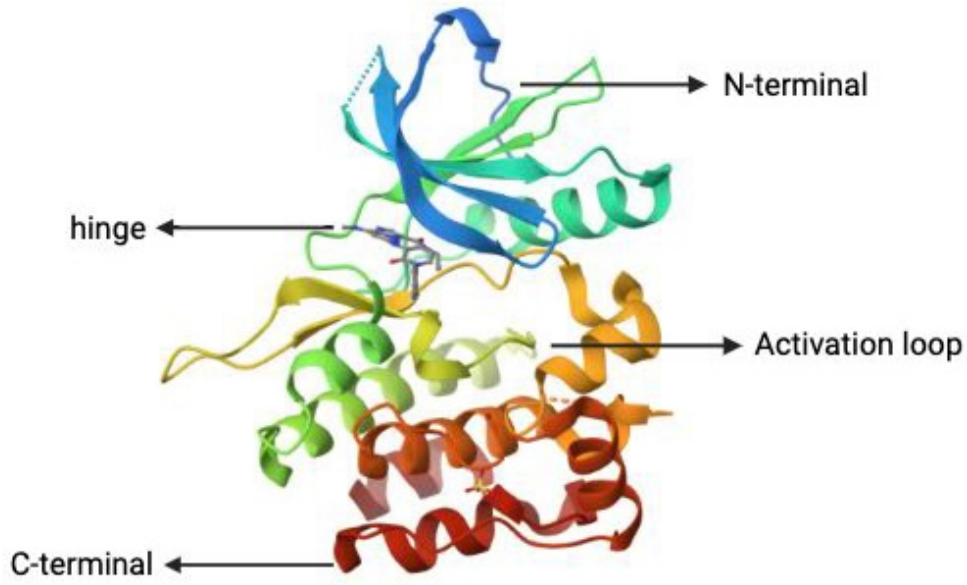


Figure 1: Typical Tyrosine Kinase receptor. (PDB Code: 6NSL) (Thomas, 2013)

In figure 1 a typical tyrosine kinase receptor is showed. There is a blue lobe at the N-terminus and a red lobe at the C-terminus. The activation loop ends are depicted in yellow. The hinge region is shown in color green. (Thomas, 2013)

1.4 A Brief Summary on Tyrosine Kinase 2

Tyrosine kinase 2 is an enzyme that plays a role in cytokine signaling; it belongs to the Janus kinase family of non-receptor tyrosine kinases. However, since TYK2 operates downstream of growth factor receptors which are often hyperactivated in cancer inhibiting it may have therapeutic advantages for cancer treatment. (Übel C. M., 2013) In cancer, tumor formation, and treatment response, TYK2 plays a complex role. Multiple cancer cell lines have shown TYK2 overexpression, and a mouse model deficient in this protein is more likely not to develop cancers.

1.5 Overview on Family of Tyrosine Kinase 2

One of the most significant families of intracellular protein tyrosine kinases is the Janus kinases (JAKs), which include four members in mammals: JAK1, JAK2, JAK3, and TYK2. So, basically Tyrosine kinase 2 belongs to JAKs family. (Lucet I. S., 2006)

In figure 2 the classification on family of PTK is given below:

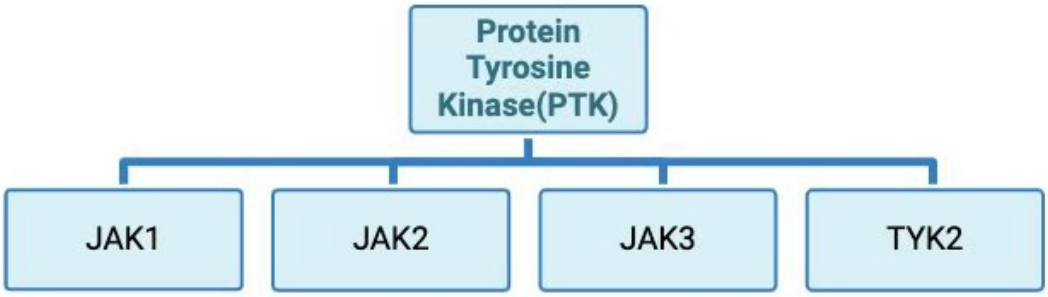


Figure 2: Family of TKY 2

On a global scale, 11 JAK inhibitors can be found, broadly classified into two groups. One kind of JAK inhibitor hits multiple sites simultaneously; these are called non-selective JAK inhibitors. The therapeutic field they operate in is wide. Even though they work quite well, they disrupt natural pathways and have serious negative side effects (Min, 2015). (Lucet, 2006)

1.6 Functions of Tyrosine Kinase 2

Intracellular tyrosine kinase 2 mediates pathways for immunological and inflammatory signaling. In innate and adaptive immune cells, TYK2 plays a crucial role in regulating immunological responses. From the figure 3, we can see that most of the functions of TYK2 are related to cancer as well as autoimmune diseases. TYK2 is involved signaling transduction of cytokines, they also have tumor promoting effects, also play a role in cell growth, proliferation and survival which connects it to cancer. (Owen, 1996) TYK2 also transmits signals and regulate immune cell functions and immune responses, TYK2 also contributes to

the regulations of inflammatory responses by controlling the production of pro-inflammatory cytokines which connects it to the autoimmune disease. That is the reason TYK2 is becoming a major target for a lot of human diseases. (Carmen Avendaño, 2008) (Ghoreschi K, 2009)

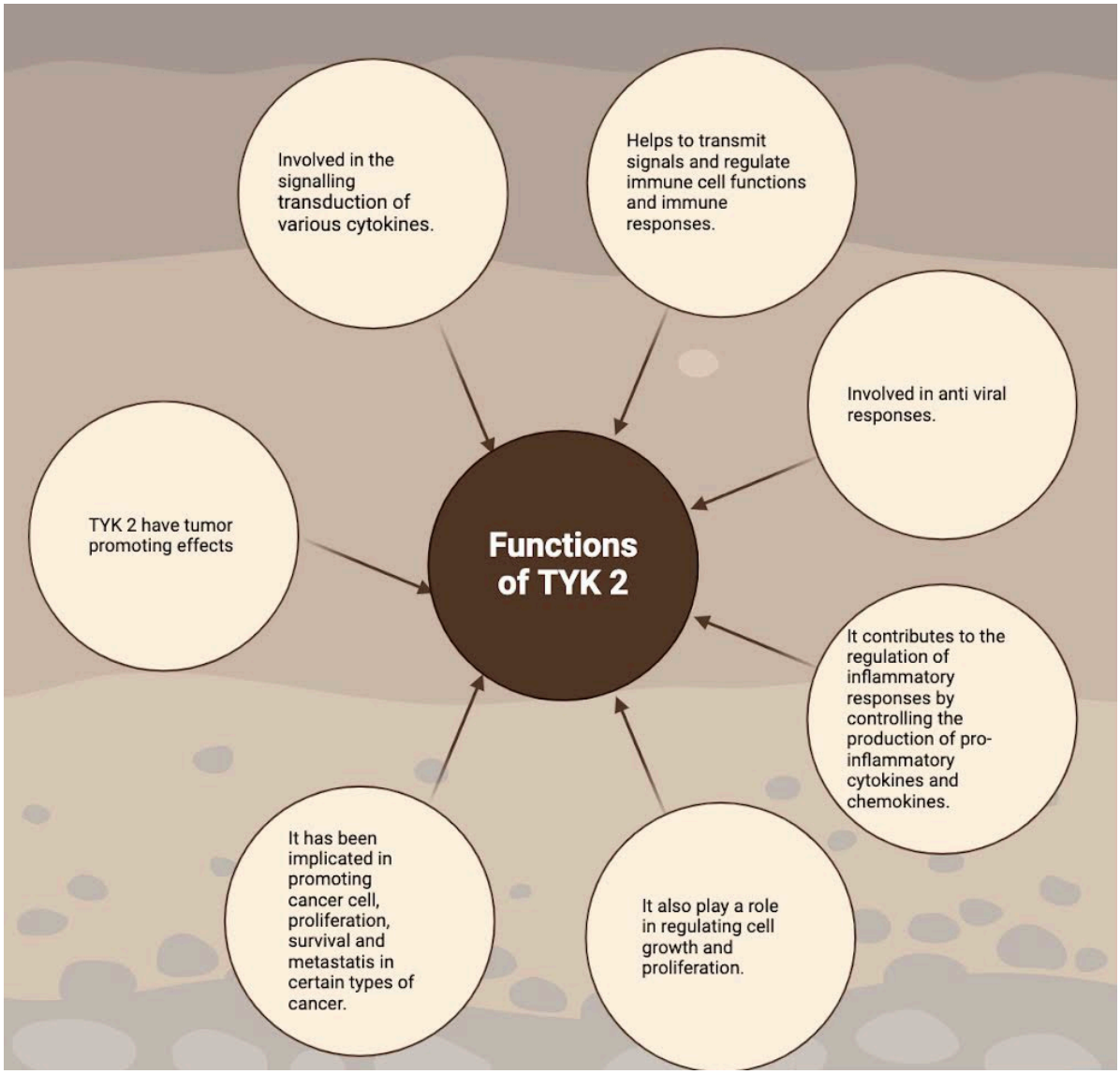


Figure 3: Functions of TKY 2

1.7 Role of Tyrosine Kinase 2 in Cancer

A large amount of research has focused on the roles of TYK2 and other JAKs in cancer. All cells, normal and cancerous alike, rely on JAKs for several cellular processes, including proliferation, differentiation, survival, and death. (Rane SG, 2000)

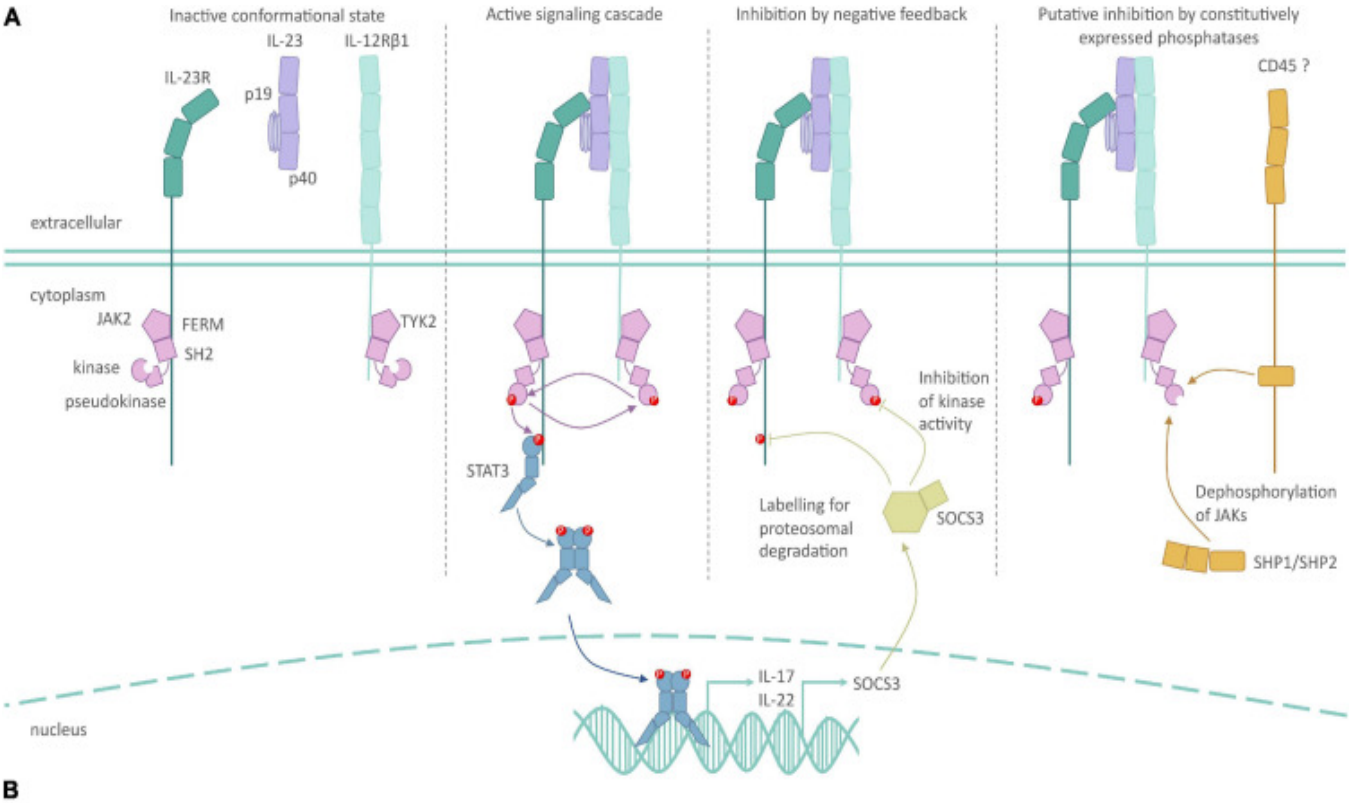
Prostate malignancies, squamous cervical carcinomas, and a number of human breast cancer cell lines have all been found to overexpress TYK2. (Ide H, 2008)

Another study has shown TYK2 capabilities that justify their evaluation as potential new targets in treatments meant to lessen chemoresistance. In the case of TYK2, which is phosphorylated downstream of the FGF2 receptor, cannot proceed until extracellular signal-regulated kinase (ERK)1/2 is fully phosphorylated. Reducing FGF2-mediated proliferation and increasing chemotherapy-induced cell death in tumor cells is achieved through RNA interference (RNAi) inhibition of JAK1, JAK2, or TYK2. Unlike the conventional JAK-STAT signaling pathway, this one works on its own. It is really believed that additional kinases involved in FGF2-mediated chemo resistance interact with TYK2. Furthermore, TYK2 is required for the induction of anti-apoptotic proteins including MCL-1 and BCL-2. Thus, JAK inhibitors are likely more effective in cancer treatment, as TYK2 and other JAKs play a crucial role in regulating FGF2-driven cell survival. (Carmo CR, 2011)

Despite increased MDSC activity, TYK2-deficient mice seem to have a diminished CD8+ T-cell antitumor response. Hence, to identify its precise role in cancer, TYK2 expression in tumor cells must be thoroughly investigated. Data from humans, mouse models, and cell lines all show clear differences. (Chrencik JE, 2010)

In figure 4 the function of TYK2 in IL-23 receptor signaling is showed. (A) At steady state, the FERM and SH2 domains of inactive JAK2/TYK2 bind to the intracellular domain of the matching cytokine receptor subunit. One way that JAK becomes inactive is through the

suppression of the kinase domain by pseudo kinase domains. The binding of IL-23 unites its separate cytokine receptor subunits, which causes a conformational change in JAK2/TYK2 that permits their kinase activity. Once JAKs and cytokine receptor intracellular domains are phosphorylated, the STAT3 transcription factor can be recruited and activated, leading to an increase in gene expression. An important component of the inducible regulation of IL-23 is the SOCS family of proteins, which have the ability to bind to JAKs and inhibit their cytokine function.



B

Cytokine	IL-23		IL-12		IFN-I		IL-10		IL-22		IL-13	
Receptor chain	IL-12Rβ1	IL-23R	IL-12Rβ1	IL-12Rβ2	IFNAR1	IFNAR2	IL-10R2	IL-10R1	IL-10R2	IL-22R	IL-13Rα1	IL-4Rα
Associated JAK	TYK2	JAK2	TYK2	JAK2	TYK2	JAK1	TYK2	JAK1	TYK2	JAK1	TYK2	JAK1
Major transducer	STAT3		STAT4		STAT1 and STAT2		STAT3		STAT3		STAT6	

Figure 4: TYK2's role in the signaling of IL-23 receptors. (Dominika Hromadová, 2021)

Additionally, they can tag JAKs for ubiquitin-mediated degradation. While phosphatases like SHP1 and CD45 do constitutive inhibition of JAKs, their role in IL-23R has received little attention. (B) Selected cytokines connected to TYK2 and the relevant intracellular signaling molecules and receptor subunits. The appropriate cytokine's primary STAT is displayed, but the use of STAT can differ among cells and situations. (Dominika Hromadová, 2021)

1.8 Disorders linked to Tyrosine Kinase 2

Tyrosine kinase 2 is inked with cell proliferation, cell survival and cell growth and for these functions it is connected to a lot of diseases and also it can be a great target for the treatments of these diseases. Figure 5 shows numerous human diseases, such as cancer, diabetes, autoimmune disorders, psoriasis, tumors and many others, are associated with tyrosine kinase 2. (Paul,2012) Overexpression of TYK2 is associated with an increased risk of breast, cervical, and prostate cancers. (Caroline Übel, 2013)

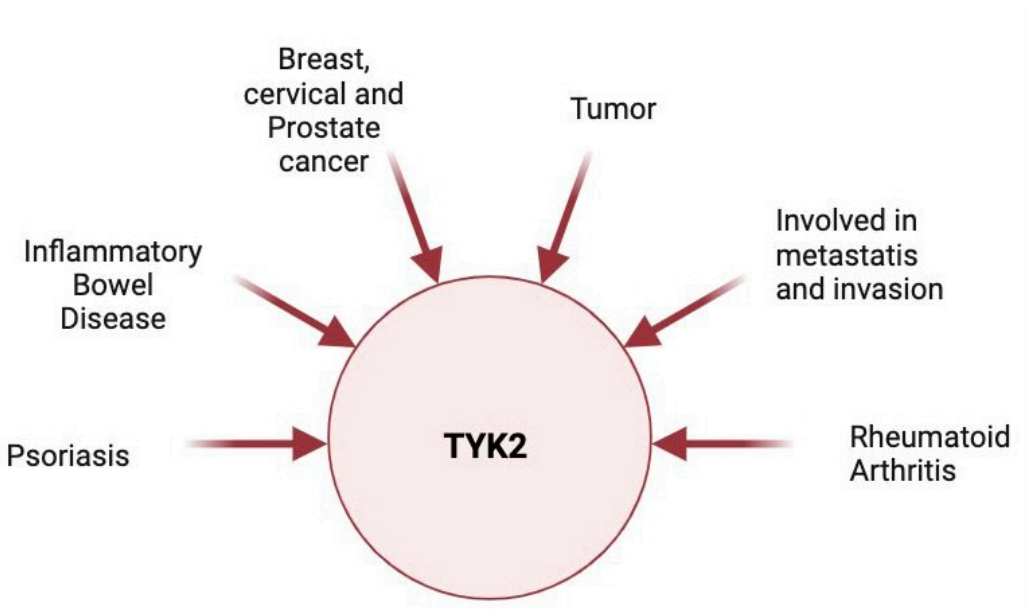


Figure 5: Involvement of Tyrosine Kinase 2 in diseases.

1.9 Significance of Tyrosine Kinase 2 in Cancer

TYK2 is a potent target, if is inhibited then it can be used in variety of diseases as a treatment. Among the diseases cancer is one of them and its new findings is that TYK2 inhibitors has a role in cancer. (Borcherding, 2021) There are a lot of TYK2 inhibitors in the market and among them some are showing potency towards cancer as inhibition of TYK2 can significantly stop the progression of cancer. Existing inhibitors are showing activity towards cancer but they are showing some drawbacks such as resistance, adverse effects also issue in selectivity. That is why further research is needed for new and potent inhibitors need to be developed for better treatment of cancer. (Banfield, 2018)

1.10 Aim and Objectives of the Project

Aim

The aim of this project is to provide an updated compilation of the recent developments of existing tyrosine kinase 2 inhibitors that are available in market and also in various stages of developments and how they can be improved to prevent draw backs of the existing inhibitors for the treatment of cancer.

Objectives

The objective of this study is given below:

- To do a comparative analysis of available tyrosine kinase 2 inhibitors that are FDA approved.
- To conduct a comparative analysis of the activity, efficacy of tyrosine kinase 2 inhibitors that are in clinical and pre-clinical studies.
- To make a compilation of major limitation of existing inhibitors and pathways to overcome those limitations.

- To discuss the possible solution that can be done to identify novel inhibitors for the treatment of cancer.

Chapter 2

Methodology

The review consists of an overview of tyrosine kinase 2 and its inhibitors on cancer treatments.

All the information in this review paper were collected from peer- reviewed research articles, collected from PubMed, Elsevier, ScienceDirect, Nature, Springer, Lancet and Francis. The information prioritized were mostly from recent years and the keywords used in searching for relevant information pertaining to they include “Tyrosine kinase”, “Tyrosine kinase 2”, “Types of Tyrosine kinase 2”, “Receptor tyrosine kinase”, “Tyrosine kinase 2 inhibitors”, “Role of tyrosine kinase 2 in cancer treatment”, “Signaling pathway of tyrosine kinase 2”, Breast cancer’’, “lung cancer” *etc*. Information was gathered and referenced properly, to provide better understanding of significance of Tyrosine kinase 2 and its inhibitors in the treatment of cancer.

Chapter 3

Tyrosine Kinase 2 Inhibitors

3.1 Overview of Tyrosine Kinase 2 Inhibitors

Tyrosine kinase inhibitors (TYK2 Inhibitors) are designed to block tyrosine kinases, which are enzymes that deliver chemical signals. Due to their role in the transmission of growth signals, tyrosine kinases can be blocked to inhibit cell division and development. Tyrosine kinase 2 inhibitors have the ability to inhibit many tyrosine kinases, or just one. So basically, the TYK2 inhibitors can be selective or non-selective. (Watford WT, 2006)

3.2 Available Tyrosine Kinase 2 Inhibitors in the Market

FDA has approved many protein kinase inhibitors so far among them many tyrosine kinase 2 inhibitors was also approved for the treatment of cancer. There is selective and non-selective TYK2 inhibitors. Deucravacitinib, Ropsacitinib and Fedratinib are selective TYK2 inhibitors and Tofacitinib, Ruxolitinib, Momelotinib *etc.* are non-selective TYK2 inhibitors. (Carmo CR, 2011)

Deucravacitinib is one of the most potent TYK2 inhibitor in the market and it was approved by the U.S. Food and Drug Administration. (Anjaneya Chimalakonda 1, 2021). Tofacitinib and Ruxolitinib are also a non- specific TYK2 inhibitor which indirectly affect the JAK/STAT pathway which TYK2 is also involved. (Jun Liang, 2023). Another TYK2 inhibitor that is being developed for the treatment of cancer and psoriasis is BMS-986202. (Chunjian Liu, 2021)

These inhibitors are mostly indicated for autoimmune diseases, psoriasis but further research showed that they have great potency in the treatment of cancer. Among them some are already approved for the treatment of cancer such as Deucravacitinib is indicated for breast and lung cancer, Momelotinib is indicated for metastatic pancreatic cancer, Tofacitinib is indicated for lung cancerand fedratinib for neoplasm *etc.* and some are in the clinical trials such as Ropsacitinib and BMS-986202 *etc*. (Thomas A. Hamilton, 1998) The inhibitors and their indications, activity and other information's are summarized below in the table:

Table 1: Summary of Tyrosine Kinase Inhibitors Available in market. (Srdan Verstovsek 1, 2023) (Chunjian Liu, 2021) (Jun Liang, 2023) (Miguel Nogueira1, 2020)

Name and Year Approved	Indication	Activity (IC_{50})	Brand Name	Reference
Deucravacitinib (2016)	Treatment for breast, lung and kidney cancer. Tumor, autoimmune disease. Psoriasis.	TYK2:1.0nM	Sotykto	(Gillooly K, 2016)
Momelotinib (2023)	Anemia, Myelofibrosis, Splenomegaly, Metastatic Pancreatic Cancer, Lung cancer.	JAK1:11nM JAK2:18nM	Ojjaara	(Srdan Verstovsek 1, 2023)

Ruxolitinib Phosphate (2011)	Myelofibrosis, Polycythemia vera, Graft vs host disease.	JAK1:3.3nM JAK2:2.8nM	Jakafi	(Jun Liang, 2023)
Tofacitinib (2012)	Lung cancer, Moderate to severe rheumatoid arthritis, psoriatic arthritis, Ulcerative colitis	JAK:1nM JAK2:20nM JAK3:112nM	Xeljanz	(Jun Liang, 2023)
Fedratinib (2019)	Neoplasms, Hemic and Lymphatic disease, solid tumor and other disease.	TYK2:3 nM	Inrebic	(Chunjian Liu, 2021)

Deucravacitinib:

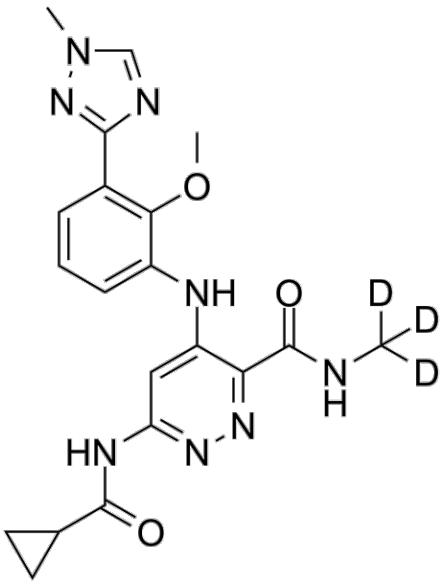


Figure 6: Deucravacitinib Structure (Gillooly K, 2016)

A TYK2 inhibitor known as Deucravacitinib (BMS-986165) is considered to be the most advanced. Figure 6 shows the chemical structure of Deucravacitinib and it was approved in 2016 and it blocks receptor mediated TYK2 activation by stabilizing the regulatory JH2 domain. It inhibits IL- 12/23 and type I IFN pathways. (Gillooly K, 2016).

Ruxolitinib:

The medicine Ruxolitinib (Figure 7), sold under the trade names Jakafi in the US and Jakavi outside the US, contains the active pharmaceutical ingredient (API) Ruxolitinib phosphate. Some myeloproliferative neoplasms (MPNs) and associated disorders can be treated with the Ruxolitinib. Ruxolitinib phosphate inhibits the JAK-STAT signaling pathway, an important regulator of hematopoiesis and immunological function. (Alexandra Coomans de Brachène1, 2020)

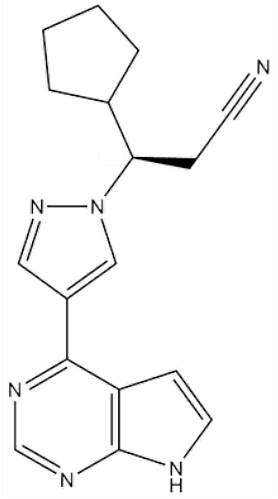


Figure 7: Ruxolitinib Structure (Alexandra Coomans de Brachène1, 2020)

By obstructing this pathway, Ruxolitinib controls abnormal cell proliferation and reduces inflammation in diseases including myelofibrosis and polycythemia mellitus. (Alexandra Coomans de Brachène1, 2020)

Tofacitinib Citrate:

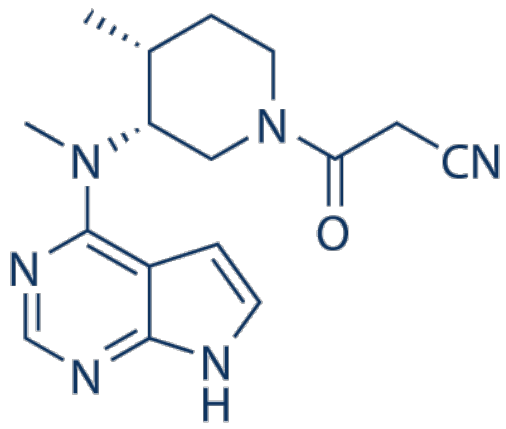


Figure 8: Tofacitinib Citrate structure (Hua Xu, 2019)

From figure 8 we can see the chemical structure of Tofacitinib Citrate which is a non- selective TYK2 inhibitors. The US Food and Drug Administration approved tofacitinib as a second-line treatment for moderate to severe RA in adults on November 6, 2012, after a comprehensive Phase II and III program with the drug was finished. Then it was approved in 25 March, 2013. Tofacitinib citrate is effective because it blocks the JAK-STAT signaling system. This pathway is involved in controlling inflammatory reactions and immunological responses. Tofacitinib blocks this route, making it beneficial in treating a number of autoimmune disorders and also lung cancer. Rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, and juvenile idiopathic arthritis are some of the conditions that benefit greatly from its use. (Hua Xu, 2019)

Fedratinib:

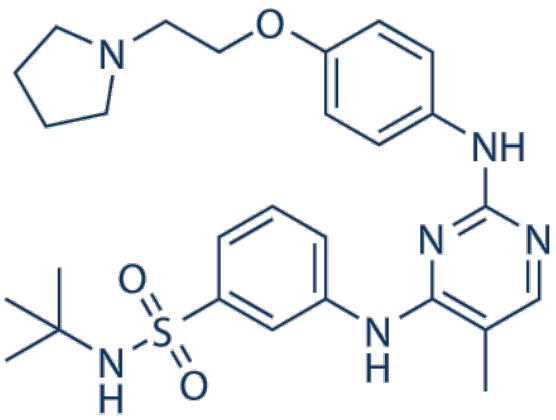


Figure 9: Fedratinib structure (Chunjian Liu, 2021)

Figure 9 shows the chemical structure of TYK2 inhibitor Fedratinib. The rare bone marrow condition known as myelofibrosis can now be treated with Fedratinib, a non-selective inhibitor of Janus kinase 2 (JAK2). Although it mostly targets JAK2, it does show modest activity against TYK2. Therefore, it can be said that it is a TYK2 inhibitor, however a less selective one. (Chunjian Liu, 2021)

Momelotinib:

Momelotinib (figure 10) is an inhibitor of tyrosine kinases that mainly targets Janus kinase proteins JAK1 and JAK2. Momelotinib is a non-selective inhibitor of TYK2. By blocking these kinases, inflammation can be reduced, aberrant cell proliferation can be controlled, and illness symptoms can be alleviated. (inger JW, 2019)

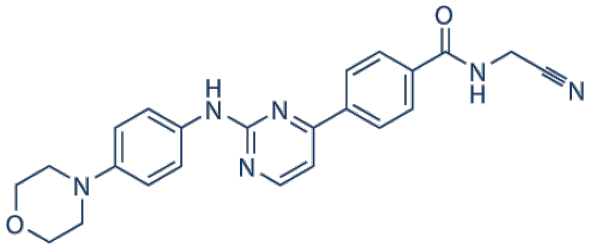


Figure 10: Momelotinib structure (inger JW, 2019)

Momelotinib is indicated for some autoimmune disorders and Lung cancer, metastatic pancreatic cancer. (Inger JW, 2019)

3.3 Tyrosine Kinase 2 Inhibitors in Clinical Phase

Only a small number of TYK2 inhibitors have made it to the clinical trial stage. (Elewaut, 2021) Among them Ropsacitinib and BMS- 986202 is showing success as a potent drug target. Ropsacitinib is in phase II and BMS-986202 is in phase I of clinical trials. (Min, 2015) The inhibitors their activity, therapeutic area *etc* are summarized below:

Table 2: Tyrosine Kinase 2 Inhibitors in Clinical Phases. (Ravi Shankar P. Singh1, 2021) (Chunjian Liu. J.-F., 2021)

Name And Phase	Therapeutic Area	Activity (IC_{50})	Reference
Ropsacitinib (Phase II)	Cancer, Infectious diseases, Skin and Musculoskeletal Diseases and other diseases.	TYK2:17nM JAK1:383nM JAK2:74nM	(Ravi Shankar P. Singh1, 2021) (Liao, et al., 2023)

BMS-986202 (Phase I)	Neoplasm, Lung cancer, Immune system Disease, Skin and Musculoskeletal Diseases, Digestive System disorder.	TYK2:0.19nM	(Chunjian Liu, 2023)

Ropsacitinib:

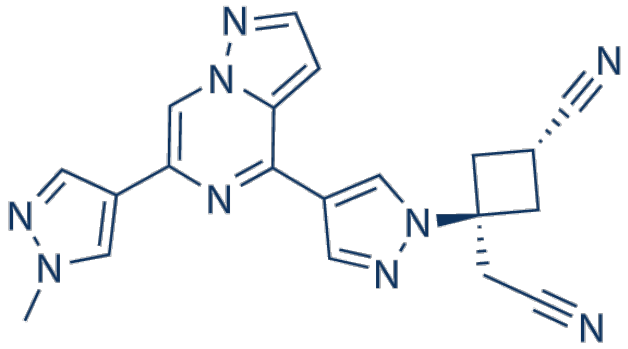


Figure 11: Ropsacitinib structure (Liao, et al., 2023)

Chemical formula of Ropsacitinib is $C_{20}H_{17}N_9$ and molecular weight is 383.419 g/mol. Ropsacitinib (Figure 11) is a selective and orally administered inhibitor of tyrosine kinase 2 with IC_{50} of 17nM for binding to TYK2 catalytically active JH1 domain. It is in clinical trials in phase 2. They also inhibit JAK1 and JAK2 with IC_{50} value of 383 nM and 74 nM. Though it inhibits JAK1 and JAK2 but still showing great potency towards TYK2. And its therapeutic areas are cancer, infectious diseases, skin and musculoskeletal diseases and other diseases. (Ravi Shankar P. Singh1, 2021) (Liao, et al., 2023)

BMS-986202:

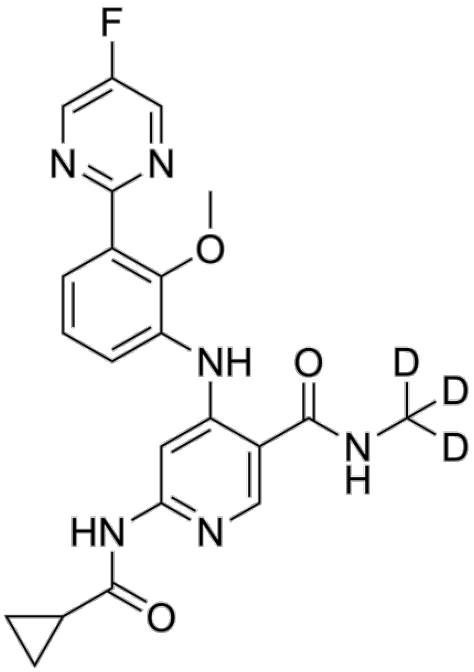


Figure 12: BMS-986202 structure (Chunjian Liu, 2023)

Chemical formula is $C_{15}H_{20}N_6O_6K$ and the molecular weight is 419.45 g/mol. BMS-986202's chemical structure is shown in figure 12 and it is in clinical trials phase I and its therapeutic areas are Neoplasm, Immune system Disease, Skin and Musculoskeletal Diseases, Digestive System disorders, Cancer. Chemical class of BMS-986202 is de novo deuterium. In vitro, BMS-986202 has been shown to inhibit the growth of cells and induce apoptosis in lung cells. The TYK2 enzyme is involved in the regulation of the immune system and inflammatory responses through the JAK-STAT signaling pathway. As a result of its ability to inhibit TYK2, BMS-986202 is thought to alleviate symptoms and reduce inflammation. There may be wider implications for cancer therapy stemming from BMS-986202's suppression of TYK2, therefore its primary development focus is on Cancer. (Chunjian Liu, 2021)

Chapter 4

Limitations of Existing Tyrosine Kinase 2 Inhibitors in Cancer

TYK2 inhibitors were developed for the treatments of various diseases such as autoimmune disease, psoriasis, tumor, cancer *etc.* but they are showing a lot of draw backs such as resistance, adverse effects, non- selectivity cardiac toxicity *etc*. (Fensome, 2018)

Some major limitations and some possible solutions are described below:

4.1 TYK2 Inhibitors can Develop Resistance

Tyrosine kinase 2 inhibitors, which are particularly important in the treatment of cancer and autoimmune illnesses, are susceptible to resistance due to a number of different processes. To start, the effectiveness of drugs can be diminished due to mutations in the TYK2 gene, which prevent inhibitor binding. (Rosenzweig1, 2018) Another possibility is that cancer cells enhance TYK2 expression, making inhibition ineffective. Bypassing TYK2 suppression and enabling cell survival and proliferation, other signaling pathways can be activated. Also, cells can change how drugs are taken in or out of the cell, which can lower the concentration of inhibitors inside the cell. (Cristian Tomasetti, 2013) Signals for survival can be transmitted by the stromal microenvironment, which can enhance resistance. Some populations may develop innate or acquired resistance as a result of epigenetic alterations and clonal evolution. (Christine M. Lovly, 2015)

4.2 TYK2 Inhibitors Causes Infections

Blocking TYK2 may result in the development of viral and mycobacterial infections, as anticipated by people who are deficient in TYK2 (inger JW, 2019) This is a problem that might arise from using this method. Respiratory and nasopharyngeal infections were more common, suggesting that TYK2 inhibition increased susceptibility to viral infections. In the studies with deucravacitinib, mycobacteria infections were not found; nevertheless, respiratory infections were more common. Recall that a group of knowledgeable individuals was just formed to assess the current state of knowledge on JAKi and to guide its application to the treatment of rheumatic diseases. (Nash et al., 2020). This study found that significant infections do occur with JAKi at a rate that is similar to that with TNF inhibitors, when considering the available safety profiles. Only tofacitinib, when compared to TNFi, has been demonstrated to raise the risk of infection in patients 65 and older. (Lortholary et al., 2020; Nash et al., 2020).

4.3 TYK2 Inhibitors Causes Cardiovascular Dysfunction

Cardiovascular impairment due to TYK2 inhibitors are connected with a number of risk factors. Heart disease (CAD), advancing age, hypertension (HTN), diabetes (DM), and tobacco use are all factors that can increase a patient's risk. Inflammation markers in the blood, including high-sensitivity C-reactive protein (hs-CRP), interleukin-1 (IL-1), interleukin-6, and fibrinogen, can help detect other risk factors, such as the likelihood of atherothrombotic events. As additional risk factors, an increased concentration of cardiac biomarkers like hsTnT, NT-proBNP, MR-proANP, MR-proADM, and C-terminal pro-endothelin-1 is analyzed. In all, 116,117 Patients with cancer whose levels of these indicators are high before cardiotoxic treatment begins have a higher risk of dying from any reason. (Shyam Sunder, 2023)

4.3.1 Cardiac Surveillance in Patients Receiving TYK2 Inhibitors

Patients who are taking TYK2 inhibitors should have their hearts monitored. At this time, there is no defined protocol that can be utilized for surveillance purposes. When it comes to patients who are being treated with TYK2 inhibitors for VEGFI and BCR-ABL, it is recommended that an ECHO be performed at least once every four months for the first year. An early assessment, on the other hand, is performed two to four weeks following the beginning of medication therapy for individuals who are considered to be at high risk. In patients who are taking long-term therapy and who do not experience any symptoms during the first year, an electrocardiogram (ECHO) can be performed every six to twelve months after that. Additionally, the levels of '27,120' BCR-ABL TYK2 inhibitors are enhanced when they are provided concurrently with CYP3A4 inhibitors such diltiazem and verapamil. This is because CYP3A4 is the primary enzyme responsible for their metabolism. Nilotinib and ponatinib are two examples of BCR-ABL TYK2 inhibitors that are increasingly being linked to peripheral atherosclerosis. With a value of less than 0.9, the Ankle Brachial Index (ABI) is a highly sensitive and specific diagnostic tool, specifically identifying peripheral artery disease. In accordance with the recommendations provided by European Leukemia Net, ABI (or duplex ultrasonography) analysis is performed every six to twelve months.

For the chemotherapy regimen, the medications that are used should be chosen based on the effects that they are known to have on cardiovascular disease that was already present. In the event that a cardiotoxic medication is being administered, it is imperative that the pre-existing comorbidities be effectively managed. As an illustration, the HER2 targeted procedure was paused that can be continued once the LVEF has been improved. (Shyam Sunder, 2023)

Chapter 5

Discussion

The discussion over tyrosine kinase 2 (TYK2) and its inhibitors in the context of cancer is a complicated and ever-evolving debate that offers a great deal of promise for the eventual treatment of cancer. There are numerous signaling pathways that are associated with cell growth, differentiation, and immunity, and TYK2 is a member of the Janus kinase (JAK) family. It plays a crucial part on these pathways. As a result of the fact that dysregulation of TYK2 has been linked to the etiology of a wide variety of cancers, it is an excellent target for medicinal research and development. (Paul, 2012)

With the intention of specifically inhibiting TYK2 activity and disrupting signaling cascades that are associated with cancer, the development of TYK2 inhibitors represents a new approach to the treatment of cancer. Because of their ability to target cancer cells while also having the potential to damage those cells, TYK2 inhibitors have the potential to be used as a therapeutic agent. This would result in a reduction in the adverse effects that are associated with chemotherapy. (Cohen, 2021)

TYK2 inhibitors have been showing promising results in the treatment of cancer and these inhibitors are also showing potency in the evaluation of clinical trials, and the results have showed promising results demonstrating their efficacy and safety in treating certain malignancies. However, in order to properly transfer TYK2 inhibitors from the laboratory to the clinical setting, it is necessary to address a number of difficulties, including off-target issues and the establishment of resistance mechanisms. (Madhusudan, 2004)

Due to the advancements in comprehending TYK2's function in various cancer sites, forthcoming studies will center on deciphering the intricacies controlled by TYK2.

Additionally, in order to customize these treatments on the specific needs of individual patients, it will be necessary to make efforts to develop accurate biomarkers that may be used to stratify patients and predict their response to TYK2 inhibitors. (Choudhury & Bhargava, 2007)

When TYK2 inhibitors are incorporated into cancer treatment regimens, there is the possibility that a new era of precision medicine will begin. This is because treatments will be tailored to the characteristics of the tumor. An approach that is deserving of additional research is the exploration of a combination therapy, which may involve the use of TYK2 inhibitors in conjunction with other medicines or immunosuppressive drugs. (Borcherding, 2021)

In the future, developments in drug design and technology may result in the creation of TYK2 inhibitors that are more powerful and selective, which would result in an increase in the therapeutic efficacy of these potential medications. The decision of whether or not to accept TYK2 inhibitors as standard or adjuvant therapy in the treatment of various types of cancer will be based on how well they perform in clinical studies and the approval process. (Chrencik JE, 2010)

The dispute around TYK2 and its inhibitors in cancer shows that there is room for a therapeutic approach to cancer treatment. Continuous research and clinical trials will have a significant impact on the future and will bring new opportunities for individuals who are coping with a variety of critical conditions to improve their results and modify their treatments. (Cohen, 2021)

Chapter 6

Conclusion

In conclusion, tyrosine kinase 2 (TYK2) and its inhibitors have emerged as attractive targets in the treatment of cancer, and they promise new pathways for precision medicine. TYK2 is a member of the Janus kinase (JAK) family and is shown to have a significant part in the processes of cell proliferation, differentiation, and signaling pathways that are associated with the immune system. According to research, abnormal activation of TYK2 is linked to a wide variety of cancers, which makes it an appealing target for the development of new drugs.

Within the realm of cancer research and treatment, the development of TYK2 inhibitors represents a significant step forward. Small compounds like these have the ability to specifically inhibit TYK2 activity, which in turn disrupts the dysfunctional signaling cascades that are associated with cancer. The purpose of these inhibitors is to slow the growth of tumors, induce apoptosis, and modify the immune system's response to cancer cells. They do this by targeting TYK2.

Clinical trials that have been conducted to evaluate TYK2 inhibitors have provided encouraging results that demonstrate their efficacy and safety in treating some forms of cancer. However, in order to properly implement TYK2 inhibitors into ordinary clinical practice, it is necessary to address difficulties such as resistance and the processes that cause resistance.

A new era of precision medicine has begun with the incorporation of TYK2 inhibitors into cancer treatment. This new era allows for treatments to be tailored to the particular characteristics of the tumor. It is important to conduct more research in order to completely understand the function of TYK2 in many different types of cancer and to devise therapy options that involve TYK2 inhibitors. These inhibitors have the potential to become a key

component of many cancer therapies, which would lead to improved results and positive outcomes for patients who are trying to deal with this complicated disease. As we continue to untangle the intricacy of TYK2 signaling and its implications on cancer, we will continue to make progress in this area.

Chapter 7

Future Aspects

The future of tyrosine kinase 2 (TYK2) and its inhibitors in the treatment of cancer is bright, as seen by continuous research, technical advancements, and advancements in precision medicine. (Ghoreschi K, 2009) The followings are some of the most essential aspects to consider regarding the future of TYK2 and its inhibitors in relation to cancer:

Overcoming Resistance Mechanism:

It will be essential for the future to have a solid understanding of the mechanisms that cause resistance to TYK2 inhibitors and to succeed in overcoming resistance. It is possible that the purpose of research efforts is to discover the mechanisms that are responsible for the attack and, as a result, to develop techniques that can circumvent or avoid the attack, which would delay the impact of programs that are focused on TYK2. (Brent N. Rexer, 2009)

Expansion of the TYK2 signaling network beyond its current scope:

We will be able to understand the many routes exhibited by TYK2 in different types of cancer thanks to the ongoing study presently underway. A deeper understanding of the context in which TYK2 inhibitors might be most effective requires deciphering the complex methods employed by TYK2-mediated mechanisms. (Xiaoyi Hu, 2021)

The identification of biomarkers for the purpose of patient stratification:

It is anticipated that future research will concentrate on the identification of reliable biomarkers that are capable of predicting patient response to TYK2 inhibitors. A more tailored approach to TYK2-targeted therapy will be made possible by stratifying patients based on the molecular signature of their tumors. This will allow for the optimization of treatment and the reduction of needless side effects in patients who do not react to treatment. (Manish Chand D. S., 2018)

Developments in Drug Design and Delivery:

Additional developments in drug design and technology may result in the creation of TYK2 inhibitors that are more powerful and selective, as well as those that have improved pharmacokinetic features. With the help of innovative medication formulations and delivery technologies, TYK2 inhibitors can be made more bioavailable, which could lead to a boost in their therapeutic efficacy. (Beilei Wang, 2021)

Clinical and Regulatory Considerations:

The development of TYK2 inhibitors through clinical studies and regulatory approvals will be extremely important with regard to therapeutic applications. The outcome of clinical trials that are currently underway and those that will take place in the future will determine whether or not TYK2 inhibitors will be regarded standard or supplementary therapy in the treatment of various forms of cancer. (Kuojun Zhang, 2023)

Incorporation into cancer treatment protocols:

If TYK2 inhibitors are shown to be both effective and safe, they will be adopted into cancer therapy regimens. The formulation of guidelines for the use of TYK2 inhibitors, either on their own or in conjunction with other treatments, is essential in order to guarantee the efficient application of these medications in clinical settings. (Lei Zhong, 2021)

Collaboration and Data Sharing on a Global Scale:

The future prospects for TYK2 research will entail more collaboration between researchers, physicians, and departments of pharmaceutical companies. Increasing the amount of knowledge, discoveries, and resources that are shared on a worldwide scale will lead to a better understanding of the role that TYK2 plays in cancer and the creation of vaccines that are effective. (Melissa Badowski, 2017)

The conclusion is that TYK2 and its inhibitors have a significant amount of potential for the future of cancer treatment, and that judgments regarding oncology should be based on current research. These antibodies will become therapeutic methods and offer novel ways to improve outcomes and life expectancy for cancer patients as our understanding of TYK2 biology continues to advance and clinical studies continue to reveal positive results. (Cristian Tomasetti, 2013)

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A Review on Tyrosine Kinase 2 and its Inhibitors for the Treatment of Cancer.

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