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SPECIAL ARTICLE

Lineage of drug discovery research on fluorinated pyrimidines: chronicle of the achievements accomplished by Professor Setsuro Fujii

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Abstract

Prof. Setsuro Fujii achieved significant results in the field of drug discovery research in Japan. He developed nine well-known drugs: FT, UFT, S-1 and FTD/TPI are anticancer drugs, while cetraxate hydrochloride, camostat mesilate, nafamostat mesilate, gabexate mesilate and pravastatin sodium are therapeutic drugs for various other diseases. He delivered hope to patients with various diseases across the world to improve their condition. Even now, drug discovery research based on Dr. Fujii's ideas is continuing.

Keywords Cancer chemotherapy · 5-Fluorouracil · Tegafur · Tegafur and uracil · Tegafur, gimeracil and oteracil · Trifluridine and tipiracil hydrochloride · Cetraxate hydrochloride · Camostat mesilate · Nafamostat mesilate · Gabexate mesilate · Pravastatin sodium · Senescence

Abbreviations

5-FU	5-Fluorouracil
FT	Tegafur
DPD	Dihydropyrimidine dehydrogenase
OPRT	Orotate phosphoribosyl transferase
UP	Uridine phosphorylase
TP	Thymidine phosphorylase
UK	Uridine kinase
TK	Thymidine kinase
RNR	Ribonucleotide reductase
TS	Thymidylate synthase
Urd	Uridine
dUrd	Deoxyuridine
UFT	Tegafur and uracil

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GBL	γ-Butyrolactone
GHB	γ-Hydroxy butyric acid
Gimeracil	5-Chloro-2,4-dihydroxypyridine
Oteracil	Oxonic acid
S-1	Tegafur, gimeracil and oteracil
RFS	Relapse-free survival
OS	Overall survival
FTD	Trifluridine
TPI	Tipiracil hydrochloride
FTD/TPI	Trifluridine and Tipiracil hydrochloride
BrdU	Bromodeoxyuridine

Introduction

Prof. Ken Shirabe, President of the 60th Annual Meeting of the Japan Society of Clinical Oncology in 2022, asked Dr. Yoshihiko Maehara to introduce the significant research results of Prof. Setsuro Fujii in the field of anticancer drug development in Japan, to members of the Japan Society of Clinical Oncology.

Dr. Maehara, a former student of Dr. Fujii, honored to receive this assignment, hereby introduces some extraordinary achievements of Dr. Fujii as well as some insights into the personality of this great man.

Dr. Fujii joined the Department of Medical Biochemistry after graduating from the Faculty of Medicine, Kyushu Imperial University (currently, Kyushu University) in 1949. He then studied at Yale University in the United States, and was subsequently appointed as professor of Tokushima University Faculty of Medicine in 1962 and as professor of the Institute for Protein Research of Osaka University in 1976. After leaving the position in 1984, he continued drug discovery research as the head of the Biwako Research Institute of Otsuka Pharmaceutical Co. Ltd..

Dr. Fujii passed away from disease in August 1989 and was posthumously conferred the honorary rank of Shoshii (Senior Fourth Rank) by the Japanese government.

Dr. Fujii developed nine well-known drugs during his lifetime.

Even now, drug discovery research based on Dr. Fujii's ideas is continuing.

Introduction of FT in Japan and the discovery of UFT

> "A new drug enters the world after clearing multiple hurdles. It will become a better drug if we can reveal the metabolism of the drug and adapt it."

The success story of discovery of fluorinated pyrimidine anticancer drugs represented by sequential discovery of FT, UFT, S-1, and FTD/TPI started from the above statement by Dr. Fujii.

The anticancer drug 5-FU is a drug derived from uracil of which the hydrogen at the 5-position is replaced by fluorine (Fig. 1) [1]. FT is a drug with a furan ring bound to 5-FU [2] and is metabolized to 5-FU by microsomal P450 in the liver to exert its anticancer effect [3].

The metabolic pathways of FT and 5-FU are as follows.

FT is metabolized to 5-FU by P450 in the liver, which is phosphorylated through three pathways to become FdUMP, which forms a ternary complex with TS and methylenetetrahydrofolate, thus impairing DNA synthesis. However, most of the administered 5-FU is degraded by DPD in the liver (Fig. 2).

In 1969, Yukio Kobayashi, President of Taiho Pharmaceutical Co. Ltd. at the time, visited the Cancer Research Center in the Soviet Union. Mr. Kobayashi happened to become aware of the details of a newly synthesized compound that would later be introduced to the world as FT [2]. Mr. Kobayashi immediately decided to introduce this compound in Japan based on his keen insight.

In 1970, a development meeting was held to develop FT as a new drug. This meeting was attended by nine participants including Dr. Kimura, Vice President, National Cancer Center Japan at the time, as the chairman. Dr. Maehara's former teacher, Prof. Kiyoshi Inokuchi, also attended the meeting.

Based on the basic research conducted by Dr. Fujii et al. [3], it was revealed that FT is metabolized to 5-FU by microsomal P450 in the liver, not by TP in cancer cells.

When orally administered, FT is namely absorbed in the small intestine and transported to the liver through portal blood, where it is activated to 5-FU. It was therefore concluded that FT should be developed as an oral drug, which led to the development of the world's first oral fluorinated pyrimidine anticancer drug.

In later years, the specific isoform of microsomal P450 in the liver that metabolizes FT to 5-FU was identified as

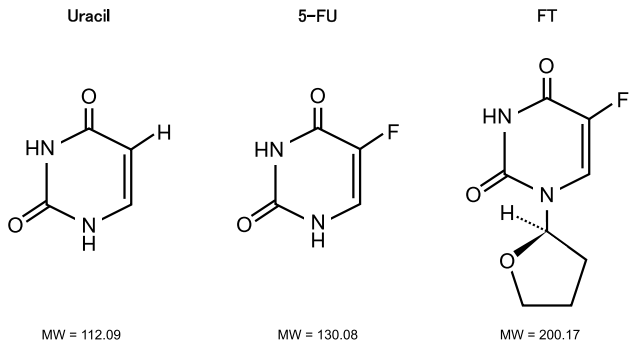

Fig. 1 Chemical structures of uracil, 5-FU and FT

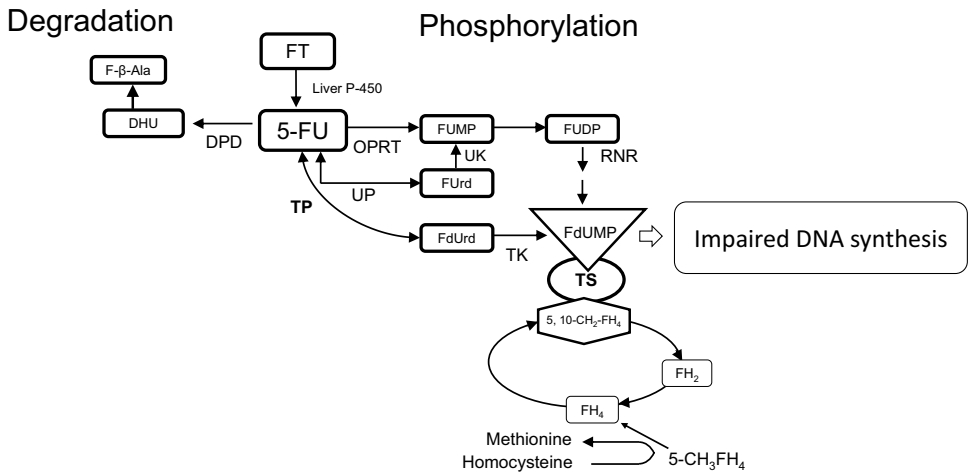

Fig. 2 Possible metabolic pathways of FT and 5-FU

CYP2A6 by Dr. Nagayama and other members of the Fujii research group [4].

In 1973 FT obtained regulatory approval in Japan as an anticancer drug for five types of cancer, namely, gastric, colorectal, breast, head and neck, and bladder cancer, and it has been used for a long period of time. At present, however, this drug has completed its role.

At the time when FT was approved for insurance coverage, Prof. Inokuchi conducted a large-scale clinical study of postoperative adjuvant chemotherapy for gastric cancer for the first time in Japan [5].

This study included 1,805 subjects from 297 institutions across Japan and reported the potential efficacy of 3-month combination therapy of mitomycin C and FT for patients with Stage III, n(+), ps(+) gastric cancer. Based on these results, it was considered that FT should be administered for a longer period than 3 months, and development of a fluorinated pyrimidine anticancer drug with higher potency was required.

Dr. Fujii then considered the metabolism of FT and reasoned that since the metabolic process after conversion of FT to 5-FU and from 5-FU to 5-FU metabolites in the liver is mainly degradation, a phosphorylation reaction may be encouraged if degrading activity is somehow inhibited.

Dr. Kazuhiro Ikenaka, et al. [6] calculated the Michaelis constant and Vmax of the metabolizing enzymes of 5-FU and uracil, and presented scientific evidence of the effect of co-administration of FT and uracil, namely that when 5-FU and uracil exist simultaneously, uracil is degraded first and 5-FU is then phosphorylated, which can lead to augmentation of the effect of 5-FU by uracil.

Dr. Fujii revealed that uracil shows a higher combined effect than Urd and dUrd when co-administered with FT, and that 5-FU shows a higher concentration in tumor tissue than blood and has high tumor specificity when the molar ratio of uracil to FT is 4:1, based on which, UFT was developed (Fig. 3) [7, 8].

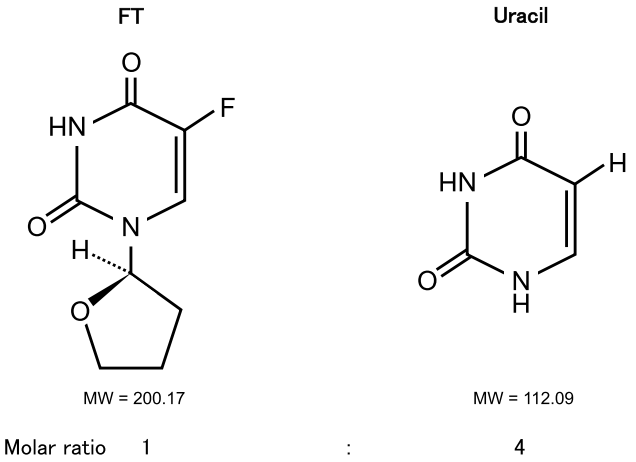

Fig. 3 Chemical structures of UFT

In 1983, UFT obtained regulatory approval in Japan for seven types of cancer (gastric, colorectal, pancreatic, lung, breast, hepatic, and gallbladder/bile duct cancer) and in 1986 for an additional four types of cancer (head and neck, bladder, prostate, and cervical cancer). This drug was also approved in foreign countries, including South Korea, Singapore, and Taiwan, and is still in use, even now.

Drs. Kato, Ichinose, Ohta, and others demonstrated the effect of 2-year treatment with UFT as postoperative adjuvant chemotherapy on the prognosis of patients with Stage I adenocarcinoma of the lung [9]. This study was conducted with a large sample size of 999 patients who underwent surgery for Stage I adenocarcinoma of the lung, and it is considered that UFT will continue to be the one and only postoperative adjuvant chemotherapy anticancer drug for Stage I adenocarcinoma of the lung in the future.

As for the reason why long-term administration of UFT for a period of 2 years is recommended, Yamada, Miyadera, et al. [10] reported the potential involvement of the long-term antiangiogenic effect of GBL and GHB, which

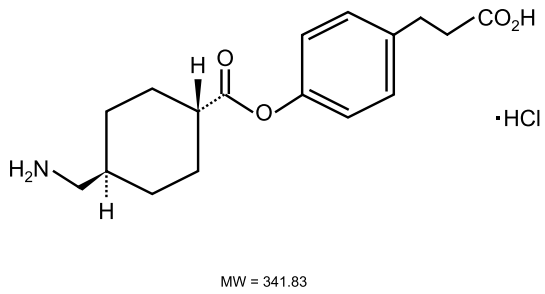

Fig. 4 Chemical structure of cetraxate hydrochloride

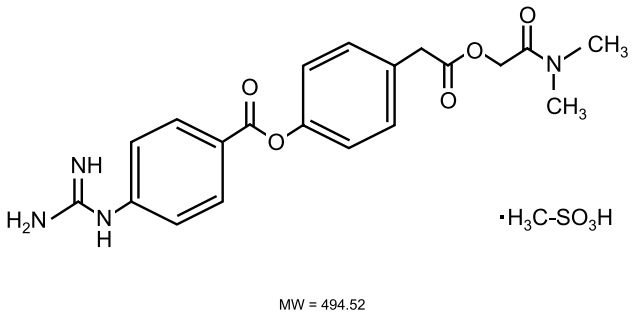

Fig. 5 Chemical structure of camostat mesilate

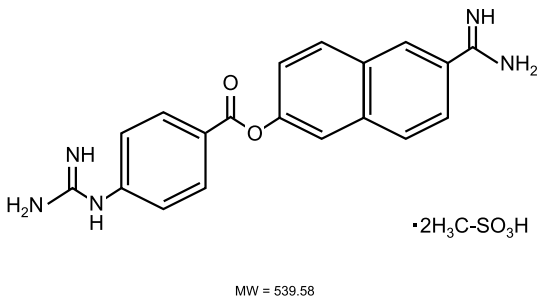

Fig. 6 Chemical structure of nafamostat mesilate

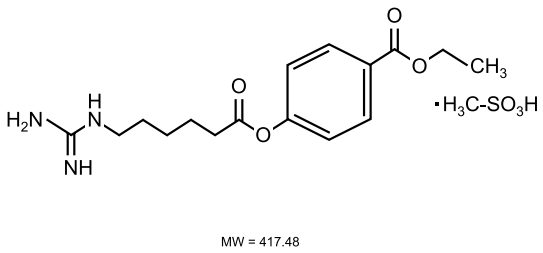

Fig. 7 Chemical structure of gabexate mesilate

are degradation products of FT, in addition to the sustained primary anticancer effect of 5-FU.

Dr. Ikenaka, who revealed the mechanism of action of UFT, was later appointed as professor of the National Institute for Physiological Sciences, and actively worked as a neurobiologist across the world [11, 12]. The institute produced 16 professors under his leadership.

Discovery of cetraxate hydrochloride, camostat mesilate, nafamostat mesilate, gabexate mesilate, and pravastatin sodium

Dr. Fujii also worked on the development/research of various other drugs in parallel with the development of UFT. In 1979, cetraxate hydrochloride obtained regulatory approval in Japan (Fig. 4). Cetraxate hydrochloride is a therapeutic drug with a mucosa-protective effect in case of gastritis/gastric ulcer, and is indicated for the treatment of gastric mucosal lesions (erosion, hemorrhage, redness, and edema) in acute gastritis and acute exacerbation of chronic gastritis and gastric ulcer [13].

In 1985, camostat mesilate obtained regulatory approval in Japan (Fig. 5). Camostat mesilate is an oral protease inhibitor that is indicated to relieve the acute symptoms of chronic pancreatitis and postoperative reflux esophagitis [14, 15].

In 1986, nafamostat mesilate obtained regulatory approval in Japan (Fig. 6). Nafamostat mesilate is a protease inhibitor that is indicated to improve the acute symptoms of pancreatitis (acute pancreatitis, acute exacerbation of chronic pancreatitis, postoperative acute pancreatitis, acute pancreatitis after pancreatography, and traumatic pancreatitis), disseminated intravascular coagulation (DIC), and to prevent coagulation of perfused blood during extracorporeal circulation in patients with hemorrhagic lesions or a bleeding tendency (hemodialysis and plasmapheresis) [16, 17].

In 1987, gabexate mesilate obtained regulatory approval in Japan (Fig. 7). Gabexate mesilate is a protease inhibitor that is indicated for various diseases accompanied by protease (trypsin, kallikrein, plasmin, etc.) disorders (acute pancreatitis, acute exacerbation of chronic recurrent pancreatitis, and postoperative acute pancreatitis), as well as disseminated intravascular coagulation [18].

In 1989, pravastatin sodium obtained regulatory approval in Japan (Fig. 8). Pravastatin sodium is an HMG-CoA reductase inhibitor that is indicated for the treatment of hyperlipidemia and familial hypercholesteremia [19–21]. Pravastatin sodium became a blockbuster drug.

All of the drugs introduced above are widely known, and are continuously used in the clinical setting, even now.

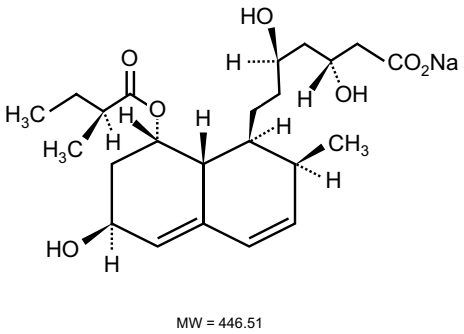

Fig. 8 Chemical structure of pravastatin sodium

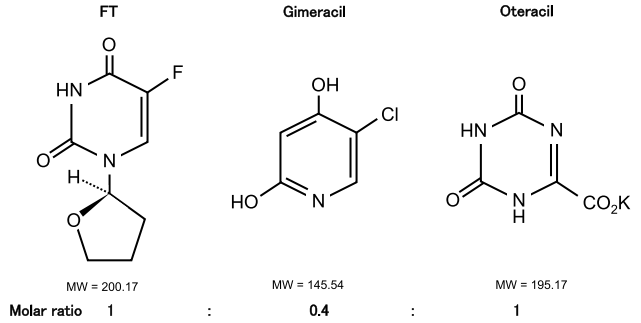

Fig. 9 Chemical structures of S-1

Discovery of S-1 as a novel 5-FU-based anticancer drug

In 1984, Dr. Fujii retired from his position at Osaka University and moved to the Biwako Research Institute of Otsuka Pharmaceutical Co. Ltd. with Drs. Tetsuhiko Shirasaka and Masakazu Fukushima to develop BOF-A2 as NeoUFT. BOF-A2 was a synthesized compound combining 1-ethoxymethyl-5-fluorouracil, a 5-FU derivative, and 3-cyano-2,6-dihydroxypyridine which has a 300-fold higher DPD inhibitory action than uracil [22, 23]. In clinical trials, BOF-A2 showed significant antitumor effects as expected [24]; however, the clinical trial was discontinued due to severe gastrointestinal side effects. While the clinical trial of BOF-A2 was under way in 1989, Dr. Fujii passed away from disease, and Dr. Shirasaka and colleagues were grieving deeply. Nevertheless, Dr. Shirasaka moved to a laboratory of Taiho Pharmaceutical Co. Ltd. with Dr. Fukushima to continue Dr. Fujii's intended drug discovery research.

Based on the experiences of patients who suffered gastrointestinal symptoms when participating in the clinical trial of BOF-A2, Dr. Shirasaka continued to consider adding a drug that can suppress the gastrointestinal side effects of the new drug, and then found oteracil.

Dr. Shirasaka et al. [25] reported that oteracil inhibits phosphorylation of 5-FU, that the orally administered drug is not detected in tumor tissue although it is distributed to normal tissues such as the small and large intestines at a high rate, and that it considerably improves pathological findings in the small intestine when administered in combination with UFT.

Then, based on the concept of augmentation of the anticancer effect of FT by using gimeracil, which has a 180-fold higher DPD inhibitory action than uracil [22] and reduction of side effects by oteracil, S-1, the world's first anticancer drug containing three compounds, was born. This drug was produced by combining FT with gimeracil and oteracil in a molar ratio of 1:0.4:1 (Fig. 9) [26, 27].

The results of an early phase II study of S-1 were reported by Prof. Keizo Sugimachi [28], and at the 36th Annual Meeting of the Japan Society of Clinical Oncology in 1998, Dr. Maehara reported the results of the phase II study of S-1 for gastric cancer. Eventually, in 1999, S-1 was approved for insurance coverage as a drug for gastric cancer.

At present, S-1 has obtained regulatory approval for seven types of cancer (gastric cancer in 1999, head and neck cancer in 2001, colorectal cancer in 2003, non-small-cell lung cancer in 2004, breast cancer in 2005, pancreatic cancer in 2006, and biliary tract cancer in 2007), and has been approved in 43 countries in the world including Japan. This drug is one of the global standard drugs in cancer treatment.

Dr. Sasako et al. [29] reported the usefulness of S-1 as postoperative adjuvant chemotherapy for gastric cancer. The position of S-1 as postoperative adjuvant chemotherapy for gastric cancer, which was the most common cancer type in Japan at the time, was established. Thus, an anticancer drug awaited by gastrointestinal surgeons across Japan was released.

Drs. Kakeji, Yoshida and others reported that postoperative adjuvant therapy with S-1 plus docetaxel was confirmed to improve both RFS and OS, and that it is recommended as the standard of care for patients with stage III gastric cancer treated by D2 dissection [30, 31].

Dr. Oki et al. [32] reported that 1-year S-1 treatment is superior to UFT with respect to RFS, and that it has therefore become a standard adjuvant chemotherapy regimen for stage II/III rectal cancer following curative resection.

Dr. Nakachi et al. [33] evaluated whether adjuvant S-1 improved overall survival compared with observation of 440 patients with resected biliary tract cancer, and found significant improvement of survival suggesting that S-1 can be considered as standard of care for resected biliary tract cancer.

Based on the endeavors of researchers all over Japan, a number of chemotherapy regimens containing S-1 were proved to be effective for patients with various types of advanced cancer, and also in cases of adjuvant setting [34–41].

Dr. Shirasaka received the Princess Takamatsu Cancer Research Fund Prize in 2003 and the Prof. Komei Nakayama Prize of the Japan Society of Clinical Oncology in 2008 for the achievement of the S-1 development.

However, Dr. Shirasaka passed away from disease in June 2020. We wish to express our respect for his profound efforts over long years.

Discovery of FTD/TPI: groundbreaking new oral therapy for cancer

S-1 can be considered as an ultimate 5-FU drug based on the concept of its action. In clinical settings, however, the problem of 5-FU resistance inevitably occurs. For 5-FU, the activity of TS, which is the target of 5-FU action, increases [42]. It was accordingly necessary to develop a drug with a different mechanism of action that is independent of TS inhibition, namely, causing DNA dysfunction (Fig. 10).

In response to this need, researchers of Taiho Pharmaceutical Co. Ltd. investigated previously published papers with the approach of learning something new from the past and found FTD, which was synthesized by Heidelberger, et al. in 1962 [43].

The clinical efficacy of FTD was limited because it is decomposed by TP immediately after it enters the living body. Therefore, Dr. Takeda and researchers of Taiho Pharmaceutical Co. Ltd. newly developed the FTD-prodrug FTC-092, which is gradually converted to FTD in the liver, and was found to be effective against murine solid tumors [44]. However, this compound was immediately converted to glucuronidated metabolites in the clinical situation and the plasma FTD level could not be detected.

The previous data of the Fujii research group show that TK activity and dTMP kinase activity in the phosphorylation of FTD and TP activity in the decomposition of FTD are extremely high in human cancer tissues. It was therefore estimated that efficient inhibition of TP could lead to tumor-specific phosphorylation of FTD, which could enable FTD to exert an antitumor effect [45]. Eventually, as a result of extensive research efforts, Dr. Fukushima and researchers of Taiho Pharmaceutical Co. Ltd. successfully accomplished synthesis of TPI, a compound that efficiently inhibits TP [46].

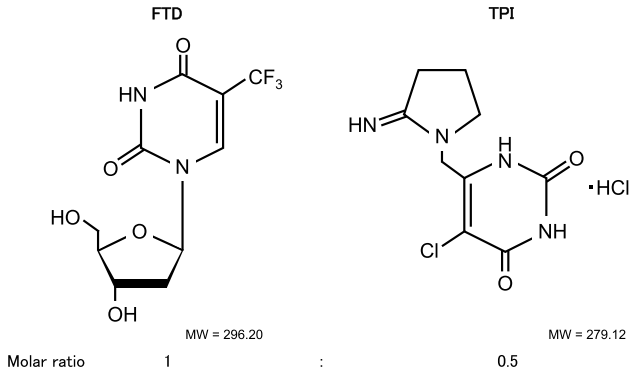

Fig. 11 Chemical structures of FTD/TPI

At the same time, Dr. Akiyama, Dr. Miyadera, and others at Kagoshima University reported that TP also exerts an angiogenic action in addition to the function of metabolizing thymidine [47–49].

It is considered that TP inhibition by TPI also causes inhibition of angiogenesis, which results in augmentation of the antitumor effect of FTD.

FTD/TPI, which was produced by combining FTD and TPI in a molar ratio of 1:0.5, was developed for use in cancer showing resistance to 5-FU (Fig. 11) [50]. Studies

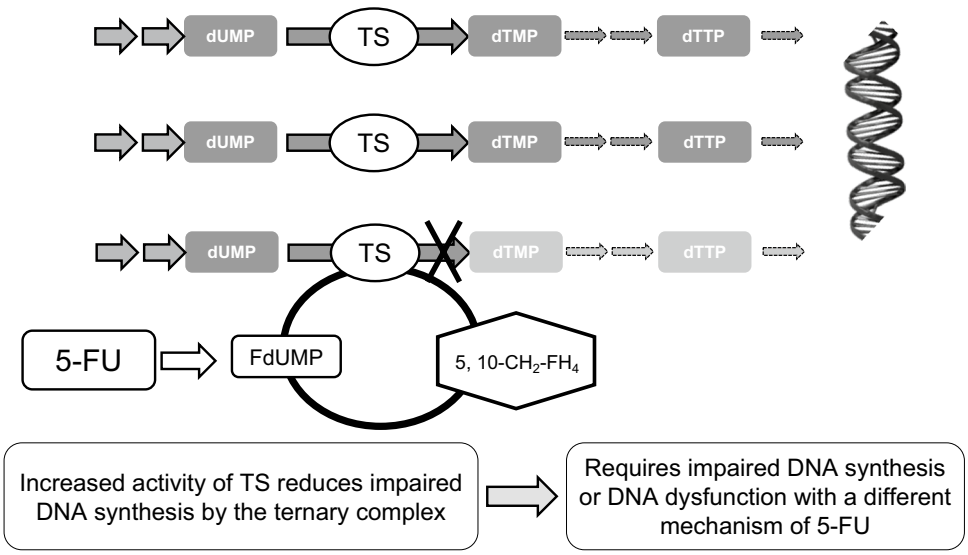

Fig. 10 Mechanism of 5-FU resistance in tumor cells

later demonstrated that this drug exerts its effect regardless of 5-FU resistance [51].

FTD/TPI obtained regulatory approval for colorectal cancer in 2014 and for gastric cancer in 2019 in Japan, and it has presently been approved in 100 countries in the world including Japan. This drug is one of the global standard anticancer drugs.

A global clinical study of FTD/TPI for advanced/recurrent colorectal cancer demonstrated its efficacy of contributing to the survival of patients [52]. Dr. Shitara et al. also reported that as treatment for advanced/recurrent gastric cancer, FTD/TPI demonstrated efficacy of contributing to the survival of patients based on the results of a global clinical study of the drug [53].

Dr. Yoshino and others reported that FTD/TPI plus bevacizumab provided significant and clinically relevant improvement in RFS and OS with tolerable toxicity in patients with chemorefractory metastatic colorectal cancer, as compared with FTD/TPI monotherapy. The combination of FTD/TPI plus bevacizumab can be a new treatment option for patients with refractory metastatic colorectal cancer and a practice-changing development [54–56].

It was later revealed that FTD can be detected by using antibodies against BrdU, that the FTD concentration in the white blood cells of patients promptly decreases when treatment has been withdrawn for 2 weeks after 2-week treatment with FTD/TPI, and that FTD absorbed by the living body can be detected tumor-specifically [57–59]. Theoretically, it can be considered that FTD/TPI is an ideal, highly tumor-specific anticancer drug.

Ongoing studies

Dr. Tokunaga et al. [60] reported that the p53 status and DNA mismatch repair function are significant factors affecting the sensitivity of cancer cells to 5-FU.

The Dr. Kitao research group is also currently conducting a study on the relationship between the morphopathology of cell death induced by FTD, the active component of FTD/TPI, and p53 status. It has been revealed that, after FTD has been incorporated into the DNA [61], p53 wild-type cells undergo senescence and p53-/- cells die by apoptosis (Fig. 12) [62].

In addition to p53-/- cells established by genome editing technology, Dr. Kitao et al. also successfully established two kinds of p53 missense-mutant cells with a mutation in the "hot spot" of the p53 gene by a knock-in method for the first time in the world. The mRNA expression profile of p53 missense-mutant cells differed largely from those of p53 wild-type cells or p53-/- cells, and we demonstrated that p53 missense-mutant cells exhibit gain-of-function property as described previously [63–65]. Despite this difference, the morphopathology of FTD/TPI-induced apoptotic cell death in p53 missense-mutant cells is quite similar to that in p53-/- cells [65].

For p53 wild-type cells, it was revealed that cellular senescence is induced by FTD and that inflammatory cytokines such as TNF-alpha are also produced. Even in such an environment, senescent cells express IAP family proteins to resist the stream of TNF-alpha-induced apoptosis signals. Therefore, it is considered a promising method to co-administer a cIAP antagonist with FTD, since

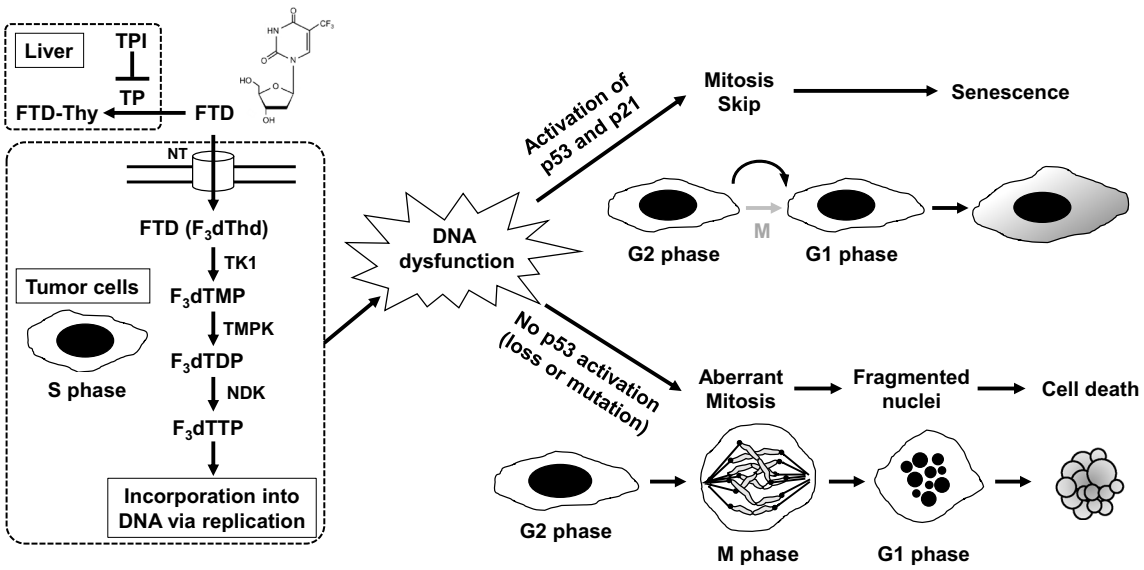

Fig. 12 Molecular mechanism of DNA dysfunction and cell death in p53-dependent manner by FTD

TNF-alpha-induced apoptosis signals may be delivered all at once, which will result in cell death (apoptosis). Thus, we are proceeding with a study of concomitant use of novel cIAP antagonists with FTD/TPI [66].

For p53 missense-mutant cells and p53-/- cells, co-administration of an ATR inhibitor with FTD achieves marked cell death. We are proceeding with a study of concomitant use of FTD/TPI with novel ATR inhibitors, with the aim of establishing a treatment method based on the molecular background of p53 in tumor cells in the future [67].

Basic research on FTD/TPI conducted so far also identified several important issues, including the properties of signals to induce cellular senescence and the strategies for their control, which are applied to normal cells and tumor cells (Figs. 13, 14). Firstly, it was possible to demonstrate that normal p53 function is essential for cellular senescence, as had been pointed out so far. Next, while studies on senolysis, an approach whereby only senescent cells die, are currently ongoing across the world in addition to our studies [65, 68–70], the experiment system of p53 activation and senescence induction led by FTD can be considered as a reliable system that can identify the process toward senescence, that is, what kind of signal should be activated after p53 activation to cause cellular senescence of tumor cells.

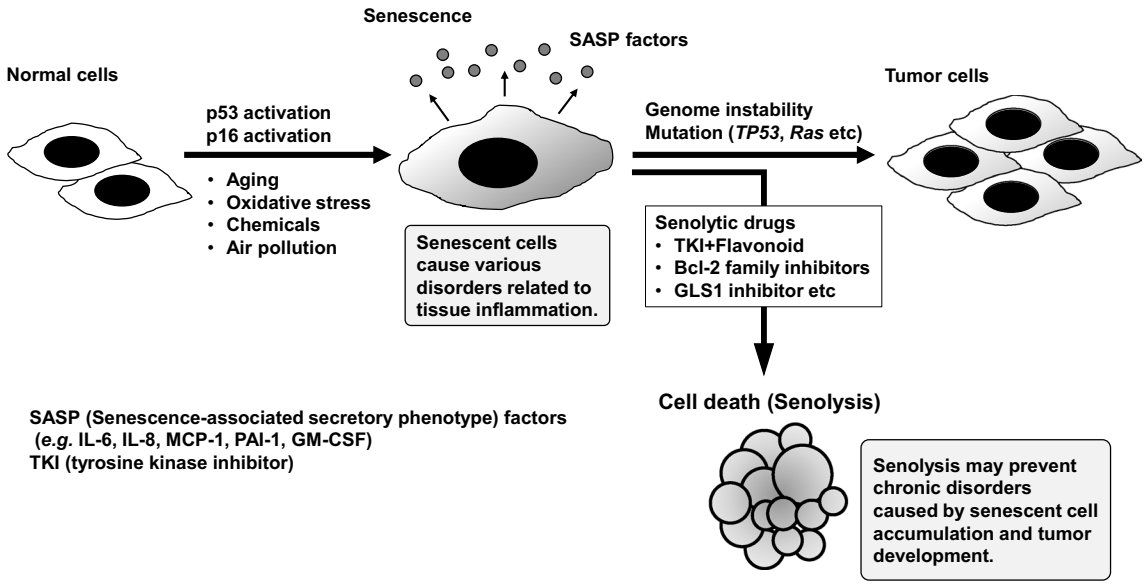

Fig. 13 Molecular mechanism of senescence in normal cells

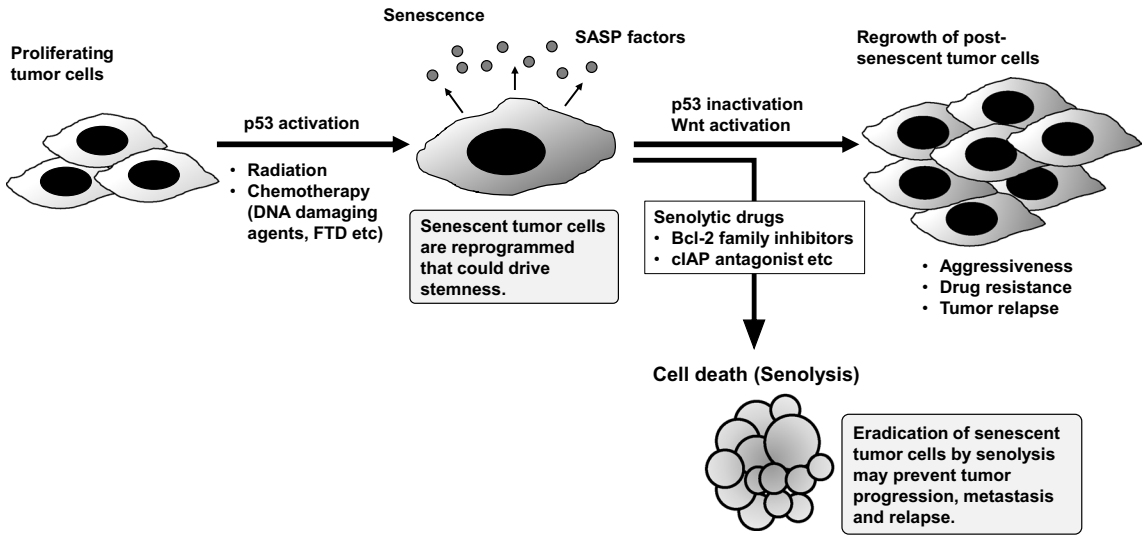

Fig. 14 Molecular mechanism of tumor senescence, regrowth and senolysis

We may thus discover an approach to prevent or delay aging in the future.

Revolutionizing cancer treatment: the profound impact of professor Setsuro Fujii's drug discoveries on global oncology

In 1981, when Dr. Maehara returned to Kyushu University after leaving Osaka University, he asked Dr. Fujii some questions:

> "Why was it possible for you to discover one new drug after the other?" to which he replied: "After graduating from the School of Medicine, Kyushu University, I entered the Department of Medical Biochemistry and learned the basics of organic chemistry in the Faculty of Science. I can imagine the three-dimensional structure of a drug based on its chemical structural formula. In this way I can consider structural formulae that will be compatible with the living body."

Dr. Fujii also said, "Chemically synthesized drugs are physically stable and such drugs can be delivered to patients who suffer from diseases across the world," "Protein is the most important component of all living organisms. Therefore, protease inhibitors are highly versatile in terms of drug effect," and "I also learned organic chemistry in the Faculty of Science, Kyushu University after entering the Department of Medical Biochemistry. Surgeons must learn various disciplines besides surgical procedures for surgical science to further evolve."

Dr. Maehara also asked him, "Why do you refrain from taking center stage even after developing a new drug?" to which Dr. Fujii answered, "The effect of a new drug is demonstrated by clinical doctors. They are facing their patients while working hard. I should therefore not take center stage, even if I have developed the drug."

Dr. Maehara realized Dr. Fujii's modesty and profound personality through these conversations.

Dr. Fujii's social contributions through drug discovery are introduced below.

Basic and clinical research of the drugs that Dr. Fujii developed continue. As of October 1, 2022, a total of 12,950 papers written in Japanese as well as 12,950 written in English, both huge numbers, have been published. It shows that the results of his research have been sublimated into a discipline.

Dr. Fujii used the financial gains he obtained for the patents of drugs he developed to establish the Setsuro Fujii Memorial, The Osaka Foundation for the Promotion of Fundamental Medical Research in 1980. Taiho Pharmaceutical Co. Ltd., established the Kobayashi Foundation for Cancer Research in 2006.

Currently, these foundations provide research grants for excellent basic and clinical research projects across Japan to promote research progress. The Fujii foundation donated a large amount of 3 billion yen to Tokushima University in 2013 following Dr. Fujii's last wishes, and this donation was used to establish the Fujii Memorial Institute of Medical Sciences, Institute of Advanced Medical Sciences, Tokushima University. This institute has three divisions (Division of Cell Signaling, Division of Molecular Endocrinology, and Division of Molecular Life Science) and an open laboratory, which has become a mecca of basic research in our country.

In the Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, to which Dr. Maehara belong, Dr. Fujii provided guidance to three generations, namely, Prof. Inokuchi, Prof. Sugimachi, and Prof. Meahara. The staff of this department have pursued their studies on basic biology in various fields as graduate students. Currently, 26 of them have been appointed as professors in various fields including surgical medicine and are working actively across Japan in 2022. Of course, Dr. Shirabe, President of the 60th Annual Meeting of the Japan Society of Clinical Oncology, is one of them.

At Tokushima University, where Prof. Fujii was professor for a long period of time, Dr. Mitsuo Shimada, who is Dr. Maehara's most accomplished colleague, has been appointed as professor of the Department of Digestive Surgery and Transplantation. Dr. Shimada has built a strongly united, active department and is conducting state-of-the-art research utilizing the open laboratory of the Fujii Memorial Institute of Medical Sciences, Institute of Advanced Medical Sciences, Tokushima University while providing safe and reliable surgical care.

Conclusion

Prof. Setsuro Fujii is a great basic biologist who developed as many as nine well-known drugs in his lifetime.

His legacy of overflowing enthusiasm and continuous efforts in basic research and drug discovery is continuing in many researchers across Japan.

I think Dr. Fujii showed his juniors, including Dr. Maehara, the ideal way of life as a life science researcher through his own behavior, and encouraged our passion for drug discovery.

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Declarations

Conflict of interest Yoshihiko Maehara, Mitsuhiko Ota, Norifumi Harimoto, Koji Ando, Ryota Nakanishi, Tetsuro Kawazoe, Yoshiaki Fujimoto, Kentaro Nonaka and Tomoharu Yoshizumi have no conflicts of interest. Eiji Oki received honoraria from Taiho Pharmaceutical Co. Ltd., Ono Pharmaceutical Co. Ltd., and Daiichi-Sankyo Pharmaceutical Co. Ltd.. Hiroyuki Kitao received research funding from Taiho Pharmaceutical Co. Ltd.. Makoto Iimori received research funding from Taiho Pharmaceutical Co. Ltd.. Eriko Tokunaga received honoraria from Daiichi-Sankyo Pharmaceutical Co. Ltd.. Hiroshi Saeki received honoraria and scholarship donation from Taiho Pharmaceutical Co. Ltd.. Yoshihiro Kakeji received honoraria and scholarship donation from Taiho Pharmaceutical Co. Ltd.. Ken Shirabe received a scholarship donation from Taiho Pharmaceutical Co. Ltd.. Hideo Baba received honoraria from Taiho Pharmaceutical Co. Ltd., Ono Pharmaceutical Co. Ltd., and Daiichi-Sankyo Pharmaceutical Co. Ltd., research funding from Taiho Pharmaceutical Co. Ltd., and Ono Pharmaceutical Co. Ltd., and scholarship donation from Taiho Pharmaceutical Co. Ltd.. Mitsuo Shimada received research funding from Taiho Pharmaceutical Co. Ltd.. Kunio Makino、Teiji Takechi、Takeshi Sagara、Kazutaka Miyadera、Kazuaki Matsuoka、Hiroshi Tsukihara、Yuki Kataoka、Takeshi Wakasa、Hiroaki Ochiiwa、and Yoshihiro Kamahori are employees of Taiho Pharmaceutical Co. Ltd. Dr. Yoshihiko Maehara has no conflicts of interest with Dr. Ken Shirabe and Japan Society of Clinical Oncology

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