Remarkable retinoids

Although there is much to be learnt about the role of retinoids in many biological functions and their potential use as therapeutics, Dr Hiroshi Fukasawa explains how these potent compounds could represent a likely candidate for the treatment for Alzheimer’s disease.

Could you discuss your background and what attracted you to this work?

When I began studying biochemistry at the Graduate School of Pharmaceutical Sciences at the University of Tokyo, Japan, molecular cloning of retinoic acid receptors (RARs), the nuclear receptors for retinoids, was one of the hottest topics in medical science. In the laboratory of Professor Koichi Shudo, who was my mentor and now my current manager, the development of novel synthetic retinoids had been pushed to the fore, and the identification and purification of RAR proteins was being carried out. I was able to participate in the project as a member of his laboratory. Although nearly 20 years have passed, studies on retinoids still bring new surprises and the importance of retinoids in mammalian life has not been fully characterised. It remains a fascinating subject for me.

What are your principal activities at the Research Foundation ITSUU Laboratory?

I joined the ITSUU laboratory in spring 2012 after spending 12 years at a drug discovery venture company. My current activities involve the management of preclinical and clinical research projects. Our achievements in these projects greatly depend on collaboration and outsourcing. Because the ITSUU laboratory is a small, non-profit facility whose strength is organic and medicinal chemistry, I am expected to play many roles: planning and coordinating projects; communicating with collaborators, doctors and contact research organisations (CROs); preparing data packages for licensing and funding and sometimes organic synthesis, if necessary. Fortunately, my previous experiences at the venture company have helped me in carrying out my mission here.

When did you first realise tamibarotene (Am80) had potential?

Am80 was developed by Dr Hiroyuki Kagechika at Shudo’s lab in the mid-1980s, just before I joined his group. The potency of Am80 in the differentiation of human promyelocytic leukaemia HL-60 cells made a strong impression on me. Am80 induced differentiation of HL-60 cells at an extremely low concentration. In addition, it was not cytotoxic, unlike many conventional anticancer agents, and seemed to restore normal differentiation of leukaemia cells. Shudo anticipated that Am80 could turn on a molecular switch in the leukaemia cells and Professor Yuichi Hashimoto proved the presence of novel nuclear proteins which specifically bind to Am80.

In 1987, molecular cloning of RARs as a novel member of nuclear hormone receptors, by Pierre Chambon and Ron Evans’s groups, proved Shudo’s hypothesis. RAR binds to specific DNA sequences of target genes and controls their expression when retinoids such as retinoic acid and Am80 bind to RAR. Afterwards, it was also elucidated that the chromosomal translocation, specific in acute promyelocytic leukaemia (APL) cells, fuses the RARγ gene to the APL gene. Literally, broken molecular switches can be compulsively turned on by high doses of retinoic acid or Am80 in APL cells.

Can you briefly explain the pathogenesis of Alzheimer’s disease (AD) and how tamibarotene may be a potential treatment?

Although amyloid β plaque formation in the brain has been considered to play a major role in causing or exacerbating AD, all the results of clinical trials of drugs aimed at preventing or slowing amyloid β accumulation were disappointing, and some scientists question whether amyloid β is the right target. Etiology and pathophysiology of AD is more complex than first thought and a multifaceted approach is necessary for curing it. For example, inflammation in the brain came to be recognised as another hallmark of AD. We propose that neurovascular dysfunction could also play a significant role in the pathogenesis of AD. In this regard, tamibarotene has a pleiotropic effect as a potential therapeutic for AD.

What results did your mouse and rat model studies yield?

We used various animal models to examine tamibarotene efficacy because no single animal model can be relevant for all aspects of AD pathophysiology. Dr Kohichi Kawahara has shown efficacy of tamibarotene in APP transgenic mice, which are genetically engineered to express an excess of amyloid-β peptides and widely used to screen for AD therapeutics. Dr Kazuyoshi Kitaoka used SAMP8 mice, which are good models for age-related memory defects; ageing is the most prominent risk factor for AD. Administration of tamibarotene into SAMP8 mice improved their behavioural abnormalities and restored abnormal sleep-awake cycles, which are often observed in AD patients. In other animal models, suppression of inflammation in the brain by tamibarotene has been shown.
New therapeutics for Alzheimer’s disease

ALZHEIMER’S DISEASE (AD) is a growing socioeconomic problem as average life expectancy increases, particularly in developed countries. Affecting mainly elderly individuals, the aetiology of AD is complex, and the cause of early onset AD also remains unclear. Genetic and environmental factors, as well as infection, may play a role and a variety of factors may also contribute to the progression of the disease. Due to this complexity, it is posited that multi-target therapies may prove to be more effective than single-target therapies in limiting the onset and progression of AD.

Drugs currently used to treat AD are neurotransmission modifiers, which only work to ameliorate symptoms. With the emergence of findings linking amyloid (Aβ) plaque formation in the brain to AD, anti-Aβ therapies, designed to reduce Aβ production or promote Aβ clearance, have been proposed.

Recent research has shown that tau protein and mitochondrial dysfunction may also be potential targets for therapy. One possible approach could be the use of multi-drug therapies, with each drug having a different target. Another possibility could be the use of a single drug that acts on a range of targets such as Aβ, inflammation and neurotransmission, involving different pathways or physiological categories.

RETINOIDS

Led by Dr Hiroshi Fukasawa, a group of researchers at the Research Foundation ITSUU Laboratory in Japan are investigating retinoids, which could prove fruitful in enhancing learning and improving memory performance amongst patients with Alzheimer’s disease. The nervous system expresses RAR, of which three subtypes (RARα, β and γ) have been identified thus far, in a spatially and temporally controlled fashion. The essential roles of RAR in normal neural development during embryonic stages have been well-studied, but even though their roles in the adult brain remain poorly understood, many studies suggest that retinoids are involved in normal learning/memory and neural regeneration.

Fukasawa enthuses: “Retinoic acid should be recognised as an essential hormone for life, as steroid hormones are. The clinical application of retinoids in neurodegenerative diseases such as AD is a new frontier in retinoid biology and a topic of social significance”.

TAMIBAROTENE

In Japan, a synthetic RARα/β agonist called tamibarotene (Am80) has been developed for the treatment of acute promyelocytic leukemia (APL). Tamibarotene has been shown to have transcriptional controls of multiple target genes involved in the aetiology and pathology of AD, and is therefore considered to be a promising candidate drug for its treatment. Fukasawa’s team and others have demonstrated in animal models that the administration of tamibarotene decreased the deposition of insoluble Aβ, ameliorated the decrease of cortical acetylcholine, reduced inflammatory cytokines; improved the recovery of spinal cord-injuries; reduced anxiety in behavioural tests; improved sleep deficits; and effected a significant improvement of memory. Tamibarotene may also improve vascular factors involved in the onset and/or progression of AD.

In previous research by another group, TTR, a carrier protein of retinol necessary for its transport into the brain, was shown to be significantly lower in AD patients than in non-dementia control individuals. It was also shown that plasma TTR is significantly lower in rapid decliners than in non-rapid decliners in AD patients, and significantly lower in moderate to severe AD patients than in mild AD patients. Therefore, it is likely that low plasma TTR levels may cause insufficient production of retinoic acid from retinol in the brain, thereby accelerating the progression of AD. Thankfully, tamibarotene can penetrate into the brain without the help of TTR.
INTRODUCTION
RETINOIDs HAVE A LEARNING FUNCTION ENHANCING ACTIVITY

OBJECTIVES
To determine if retinoids provide a novel approach for treatment of Alzheimer’s disease.

KEY COLLABORATORS
Professor Hiroshi Katsuki; Dr Kohichi Kawahara, Kumamoto University, Japan
Dr Kazuyoshi Kitaoka, University of Tokushima, Japan
Professor Kagechika, Tokyo Medical and Dental University, Japan
Professor Takami Miki, Osaka City University, Japan
Professor Fumihiko Yasuno, Nara Medical University, Japan

FUNCTION ENHANCING ACTIVITY
RETINOIDS HAVE A LEARNING FUNCTION
INTELLIGENCE

Fukasawa’s team commenced a clinical study to evaluate the efficacy and safety of tamibarotene for use in the treatment of AD as tamibarotene has been in clinical use for the treatment of APL in Japan since 2005, and has been reported to have fewer and milder side effects than other retinoids. His group is planning to use stratiﬁcation sampling for future clinical trials, selecting patients for recruitment who lack enough retinoic acid in the brain due to decreased plasma transthyretin (TTR) levels. It is hoped that the outcome of the trial will mark a breakthrough in understanding of the clinical application of tamibarotene by the researchers, which may also unlock new avenues of research.

Tamibarotene therapy has potential to be used for other neurodegenerative diseases. Candidate applications include: Parkinson’s disease, where the increase of dopamine transmission by retinoids may be helpful; multiple sclerosis, an autoimmune disease of the brain where the involvement of retinoic acid in the suppression of autoimmunity could beneﬁt patients; and spinal cord injury, for which RAR may promote neural outgrowth and neurogenesis. Because tamibarotene is rapidly excreted from the body and hardly accumulates in the brain, it is easy to control efﬁcacy and adverse events. Also, dermal toxicity commonly observed in retinoids is much less frequent in tamibarotene because it lacks afﬁnity with RARγ.

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Fukasawa is partnering with a number of other laboratories in Japan on this project and is working with many leaders in the ﬁeld, including Professor Hiroshi Katsuki and Dr Kohichi Kawahara at Kumamoto University, Dr Kazuyoshi Kitaoka at the University of Tokushima, Professor Hiroyuki Kagechika at Tokyo Medical and Dental University and Professor Takami Miki at Osaka City University. Looking to the future, he also intends to progress international collaboration with overseas scientists.

An important industrial partner for Fukasawa’s research is the pharmaceutical company Toko Pharmaceutical Industries. Tamibarotene/Am80 is now commercially available thanks to the industrial partnership, which enabled the development and manufacture of GMP-grade tamibarotene tablets for the treatment of refractory APL, and the ﬁrst clinical trials of Am80 for APL in China.

At present, Miki is leading ongoing pilot clinical trials at several sites across Japan to prove the efﬁcacy and safety of tamibarotene in mild to moderate AD patients. This involves an interventional, randomised, placebo-controlled study, in which patients receive two tamibarotene 2 mg tablets, provided by Toko Pharmaceutical, or two placebo tablets once daily for 24 weeks. Severe adverse events have not been reported. The trials are currently small-scale due to budget constraints but Fukasawa plans to focus his efforts on promoting these clinical trials and sourcing funding for larger clinical trials to further explore the untapped beneﬁts of tamibarotene for AD sufferers.

REFERENCES

For additional information please also refer to http://www.itsuu.or.jp/en/alzheimer.html