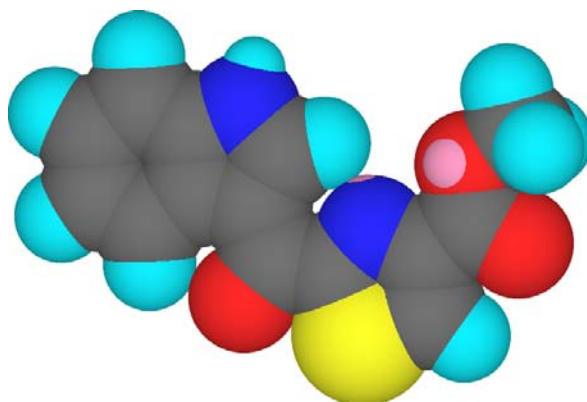


**AN EFFICACIOUS AND SUSTAINABLE YET LOW
SIDE-EFFECT THERAPY FOR CANCER, OBESITY,
AND BLINDING RETINOPATHY**



Jiasheng (Jason) Song, Ph.D.

Chief Scientific Officer
Email: jasons@ahrpharma.com
Phone: (608) 692-4791

September, 2008



AhR Pharmaceuticals, Inc.

7880 Wood Reed Dr., Madison, WI 53719, USA. Fax: (608) 848-2558
<http://www.ahrpharma.com> (web), info@ahrpharma.com (email)

TABLE OF CONTENTS

TABLE OF CONTENTS	2
1. OVERVIEW OF A NOVEL CANCER THERAPY.....	3
1-1. SERIOUS PROBLEMS WITH CURRENT CANCER THERAPIES.....	3
1-1-1. Severe side effects and toxicity	3
1-1-2. Limited effectiveness	3
1-2. A NEW PROMISING CANCER THERAPY	3
1-2-1. A Newly Discovered Natural Hormone Is Anti-angiogenic	3
1-2-2. The Natural Hormone Has other Capabilities	4
1-2-3. Multiple Fighting Strategies Make the Cancer Therapy Sustainable.....	4
1-2-4. The Natural Hormone May Offer Therapeutic Specificity.....	4
1-2-5. The Natural Hormone Is Expected to Be Low in Side Effect(s).....	4
1-2-6. Oral Administration Is A High Possibility	5
2. THE SCIENTIFIC FOUNDATION.....	6
2-1. THE ARYL HYDROCARBON RECEPTOR.....	6
2-2. A PHYSIOLOGICAL LIGAND FOR THE Ah RECEPTOR.....	7
2-3. THE INTERCONVERSION BETWEEN ITE AND ITC	8
2-4. THE THERAPEUTIC POTENTIALS OF THE HORMONE ITE.....	9
2-4-1. ITE is antiangiogenic <i>in vivo</i>	9
2-4-2. ITE has other capabilities.....	9
2-4-3. Evidence supporting the efficacy of ITE cancer therapy	10
2-4-4. Evidence supporting the specificity of ITE cancer therapy.....	10
2-4-5. Possibility of low side effect(s) from ITE therapy	11
2-4-5-1. ITE has a natural and safe way of metabolism	11
2-4-5-2. ITE should have very low chance of “off-target” action	12
2-4-5-3. No adverse effect of ITE has been observed so far	12
2-5. EASY SYNTHESIS AND ORAL ADMINISTRATION	13
3. FURTHER DEVELOPMENT	14
3-1. THE COMPANY	14
3-1-1. The board of directors.....	14
3-1-2. The initial management team.....	14
3-1-2-1. The background information about Jiasheng (Jason) Song.....	14
3-1-3. Establishment of a permanent management team	15
3-2. THE TECHNOLOGY PLATFORM.....	15
3-3. THE STRATEGY	15
3-4. THE CURRENT FOCUS	16
4. CONTACT INFORMATION.....	16
5. CITED LITERATURES.....	16

1. OVERVIEW OF A NOVEL CANCER THERAPY

1-1. SERIOUS PROBLEMS WITH CURRENT CANCER THERAPIES

There are two serious problems with current cancer therapies. The first is severe side effects and toxicity. The second is very limited efficacy. Consequently, cancer patients are still dying of the disease.

1-1-1. Severe side effects and toxicity

The majority of current therapeutic agents, in both cytotoxic and noncytotoxic category, are chemicals foreign to the human body. As a result, the body tries extremely hard to get rid of them using whatever metabolic ways available. Since our body does not have a natural and safe way of metabolizing those foreign chemicals, some nonspecific oxidation reactions then are used as major means of metabolism. The consequence is that the elimination process unavoidably generates a lot of chemically active intermediates or radicals, which will assault also normal cellular substances in the body including nucleic acids and proteins, leading to serious side effects including even the induction of new types of cancer. Since these agents are designed by humans but not the nature, they have very high chance to bind to and interact with other molecules (including proteins and receptors) than their expected targets in the body. These “off-target” bindings and interactions account for significant opportunities for side effects. The two scenarios are also true for most of the other therapies including that for obesity.

1-1-2. Limited effectiveness

The second is the effectiveness of those therapeutic agents currently in marketplace. The effectiveness of cytotoxic agents is mainly limited by their indiscriminate toxicity to normal cells and tissues so that they cannot be administered too frequently or for too long. The dosing level of those agents cannot be raised further to effectively fight cancers as one may wish due to their toxicity to normal tissues. The efficacy of noncytotoxic agents, which target specific functions important for the survival of cancers, is limited by their single mechanism based strategy. An important hallmark for cancers is their constant genetic change or mutation. Once a cancer changes into a state that it is no longer dependent on a specific function a therapeutic agent targets for survival, the efficacy of the agent will be lost immediately. The situation thus calls for the emergence of a novel therapeutic agent that can assault cancer with multiple combat strategies for sustained potency (making cancer eradication a possibility) and can be safely metabolized for low side effect(s).

1-2. A NEW PROMISING CANCER THERAPY

1-2-1. A Newly Discovered Natural Hormone Is Anti-angiogenic

We have recently discovered a new natural hormone named ITE, short for 2-(1'*H*-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester, which is a physiological ligand for a receptor called Ah (aryl hydrocarbon) receptor. We then have demonstrated that ITE is very potent in inhibiting the generation of new blood vessels from existing ones, a process termed angiogenesis, in a mouse corneal grafting model. Cancers

cannot grow further beyond 1 to 2 mm in diameter without newly generated blood vessels to supply nutrients with oxygen and remove wastes. Thus, ITE will be very effective in combating cancers by choking them off the blood supply, a technique called anti-angiogenesis. However, the hormone does not simply stop here.

1-2-2. The Natural Hormone Has other Capabilities

ITE may possess other capabilities of cancer combating. For example, ITE may inhibit cell division. Since cancer is resulted from uncontrolled cell division, ITE then may be able to stop the progression of cancers. ITE may also promote programmed cell death (apoptosis) of cancer cells. Finally, ITE may have the ability to induce cell differentiation. When cancer cells differentiate, they stop being cancer cells and therefore stop reproducing but may start dying. Additionally, ITE may be able to block actions of estrogen and androgen. Certain breast and prostate cancers are dependent on estrogen and androgen, respectively, for their sustained advancement. This capability of ITE can thus further enhance the therapy for the estrogen dependent breast cancer and androgen dependent prostate cancer.

1-2-3. Multiple Fighting Strategies Make the Cancer Therapy Sustainable

The multiple strategy backed cancer combating capability makes the ITE therapy truly unique and outstanding. The multiplicity of combating strategy is crucial in maintaining its high therapeutic potency over cancers in constant genetic change. That means we can hold cancer under control for much longer time than any other available therapies. When we can hold cancer under control for longer enough time while keep assaulting it and sending death signals to it at the same time, the cancer may eventually die off. Therefore, the multiplicity of the assaulting strategy makes therapeutic potency of ITE sustainable. The sustainability of the potency then makes the eradication of cancers finally a possibility.

1-2-4. The Natural Hormone May Offer Therapeutic Specificity

Another important issue in cancer therapy is that it is highly desirable for a therapeutic agent specifically working on cancer cells instead of normal cells. This type of specificity can be achieved if there are more target molecules the agent binds in cancer cells than in normal cells. The target molecule for ITE hormone is a cellular protein named Ah (aryl hydrocarbon) receptor (AhR). In the literature, the Ah receptor was reportedly to be highly concentrated in pancreatic cancer tissues from 14 out of 15 patients but very diluted in all normal pancreatic tissues examined. Similarly, the concentrated Ah receptor is also documented with prostate cancer. This means that the therapeutic specificity of ITE could be achieved at least in those reported types of cancer.

1-2-5. The Natural Hormone Is Expected to Be Low in Side Effect(s)

Contrary to those chemicals (used in current therapies) foreign to human body, ITE is a natural hormone produced by the human body, so the nature has designed and implemented a natural and safe way for its metabolism. Its metabolic process thus will cause less or even no problem to the body. This means that it will be very low in side effect(s). Another important reason for possible low side effect is that the binding of the

natural hormone to its receptor (the Ah receptor) is very specific and precise since it is designed and manufactured by the nature. The hormone ITE, other than those human designed chemicals, will then have low chance of binding to other proteins or molecules to provoke “off-target” problems. Low side effect(s) of ITE therapy, in turn, can be interpreted as a possibility of further raising its dosing levels to further enhance its potency. It can also be translated into a possibility of more frequent and prolonged administration, paving the way for eventual cancer eradication, an extra goal of ours.

1-2-6. Oral Administration Is A High Possibility

The hormone ITE is a small organic compound with a molecular weight of only 286 Dalton. It can be easily not only synthesized chemically but also formulated for oral administration, the most convenient route for our patients.

2. THE SCIENTIFIC FOUNDATION

2-1. THE ARYL HYDROCARBON RECEPTOR

The aryl hydrocarbon (Ah) receptor (AhR) is a ligand inducible transcription factor, member of a so-called basic helix-loop-helix/Per-Arnt-Sim (bHLH/PAS) superfamily. Upon binding to its ligand, the receptor mediates and interacts with a series of biological processes including cell division, apoptosis (programmed cell death), cell differentiation, actions of estrogen and androgen, adipose differentiation, hypothalamus actions, immune system homeostasis, vascular development and remodeling, and actions of other hormonal systems beside the expression of genes of P450 family and some others^[1-7]. The genomic action of AhR is depicted in **Fig. 1**. Once bound to its ligand, the receptor participates in biological processes through translocation from cytoplasm into nucleus, heterodimerization with another factor named Ah receptor nuclear translocator (Arnt), attachment of the heterodimer to the regulatory region termed Ah response element (AhRE) of genes under AhR regulation, and then either enhancement or inhibition of transcription of those genes.

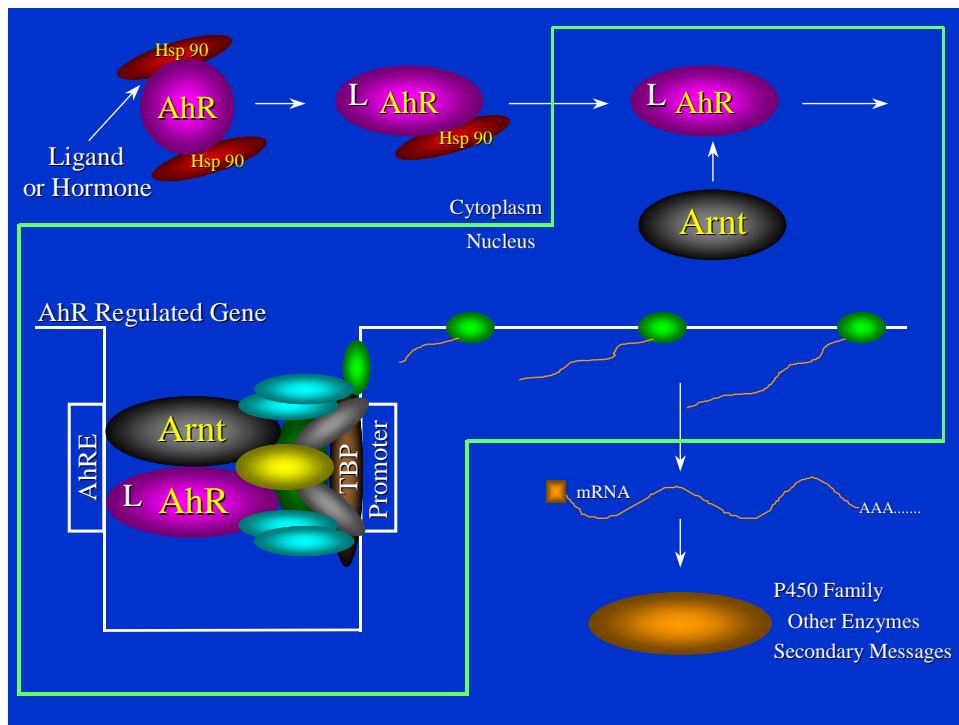


Fig. 1. The genomic action of the aryl hydrocarbon (Ah) receptor (AhR).

2-2. A PHYSIOLOGICAL LIGAND FOR THE AH RECEPTOR

The receptor system has been studied so far with its artificial ligands (exogenous chemicals that happen to have binding affinities to the receptor). While studies with those AhR artificial ligands greatly advanced our understanding toward the receptor system, thorough elucidation of the physiological roles the system plays and the potential therapeutic benefits the system may offer are impossible without the identification of AhR physiological ligand. To identify the physiological ligand for the receptor, we purified ~20 μg of an endogenous AhR ligand from lungs of ~70 adult pigs. We then unequivocally identified its previously unknown structure by means of UV, FT-IR, and mass spectroscopy; extensive nuclear magnetic resonance (NMR) spectroscopic studies; micro-scale chemical reactions, and thorough theoretical (quantum mechanical) calculations^[8]. The structure (**Fig. 2, 3A**), 2-(1'*H*-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester (short for ITE), was confirmed further by chemical synthesis^[9]. The biological potency was estimated as 5 times greater than that of β -naphthoflavone (BNF), one of the potent artificial ligands for the AhR. The estimated K_i value (the smaller the value, the higher the affinity for receptor binding) for ITE is 3 nM vs. 2 and 0.5 nM for, respectively, BNF and TCDD (another potent AhR artificial ligand).

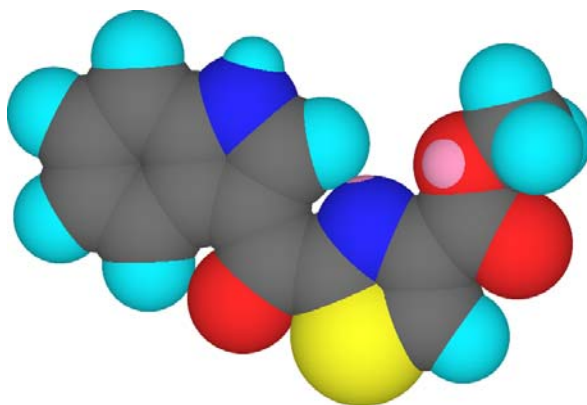


Fig. 2. The space-filling structure of ITE, a physiological ligand or natural hormone for the aryl hydrocarbon (Ah) receptor (AhR).

2-3. THE INTERCONVERSION BETWEEN ITE AND ITC

To investigate the biological production and metabolism of ITE (the AhR physiological ligand or natural hormone), we identified its precursor (or prehormone). The precursor is a carboxylate, 2-(1'*H*-indole-3'-carbonyl)-thiazole-4-carboxylate (short for ITC) (**Fig. 3**), which is unable to bind to the Ah receptor and thus inactive in the system. We also discovered an enzymatic system in animal tissue to convert ITC to ITE and an inhibitor to the conversion system. ITE was then found to be able to undergo hydrolysis into ITC catalyzed by an esterase. There is a report in literature that an esterase is inducible by an AhR artificial ligand^[10]. Therefore, it is highly possible that ITE could induce one or more esterase(s) hydrolyzing itself into ITC to establish a feedback control loop. Those discoveries lead to our current understanding toward the system as follows (**Fig. 3B**). When AhR activation is called for, the expression or activity of the enzyme(s) converting ITC to ITE will be enhanced and/or the inhibitor will be removed or inactivated to make ITE (undetectable in major adult organs including the blood) from ITC (circulating in blood). While performing other biological duties, the ITE activated receptor would also enhance the expression of one or more esterase(s) to hydrolyze ITE into ITC (inactive prehormone) to halt the action of ITE and its receptor^[11, 12].

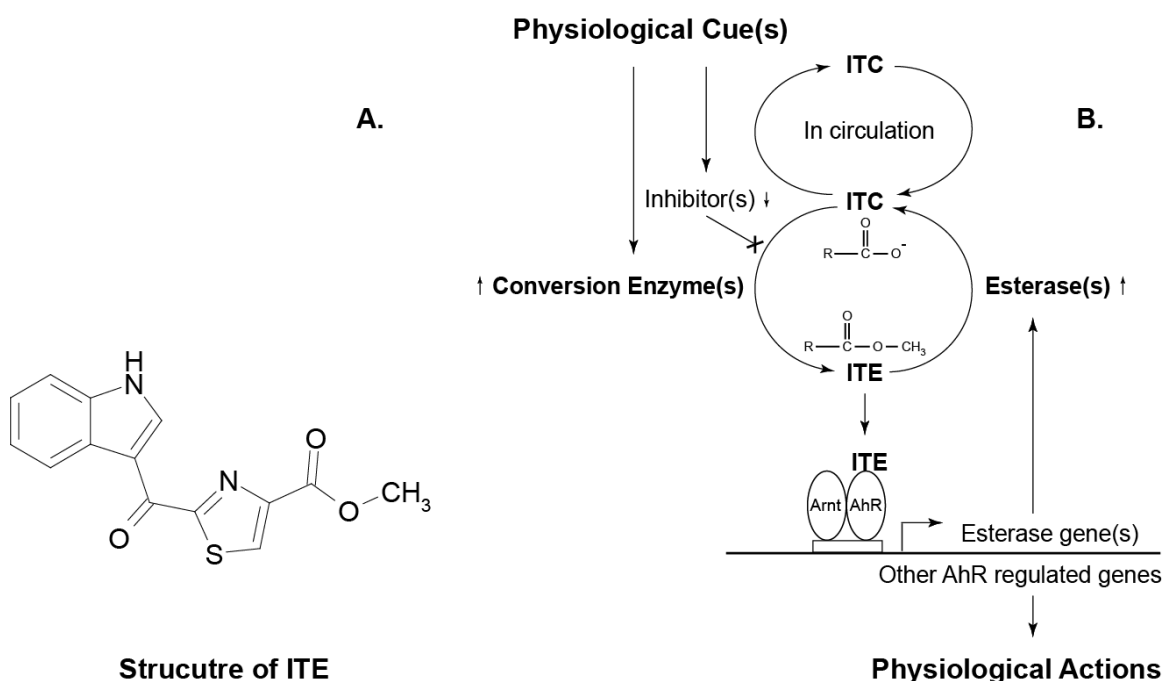


Fig. 3. The structure of ITE (**A.**) and the regulated interconversion between ITE and ITC, a precursor and also a major metabolite of ITE (**B.**)

2-4. THE THERAPEUTIC POTENTIALS OF THE HORMONE ITE

With the system of ITE and its receptor described, we will analyze the therapeutic potentials of ITE starting from its *in vivo* antiangiogenic property. Evidence of other therapeutic capabilities, the cancer therapeutic efficacy, the cancer therapeutic specificity, and possible low side effect(s) of ITE will be presented.

2-4-1. ITE is antiangiogenic *in vivo*

While we devoted most of our time and energy to the purification, identification, and confirmation of ITE and to the investigation of its biological production and metabolism, we conducted certain experiments to explore its therapeutic potentials. We discovered that ITE strongly inhibits angiogenesis (generation of new blood vessels from the existing ones) induced by both bFGF (basic Fibroblast Growth Factor) (**Fig. 4**) and tumor cells (data not shown) in a mouse corneal grafting model. With a concentration of 100 times lower (100 $\mu\text{g}/\text{kg}$ bodyweight) than that used in **Fig. 4**, ITE can still effectively block the process of angiogenesis (data not shown). This property alone is very important in combating cancer, obesity, and blinding retinopathy. Cancer cannot grow beyond 1 to 2 mm in diameter without newly formed blood vessels to supply nutrients with oxygen and remove wastes. Similar to cancer, adipose tissue expansion requires also new blood vessel generation to sustain the process. The major cause of blinding retinopathy is the excessive generation of new, but low quality, blood vessels eventually leading to blindness. ITE does not seem to stop here, however.

2-4-2. ITE has other capabilities

In addition to the antiangiogenic property, ITE may well have other capabilities. The Ah receptor (AhR) happens to be able to bind, with different affinities, to several groups of exogenous chemicals (thus artificial ligands) such as polycyclic aromatic hydrocarbons exemplified by 3-methylchoranthrene (3-MC) and halogenated aromatic hydrocarbons typified by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Known functions of the AhR thus far have been learned by probing with its artificial ligands. Analyzing data on AhR functions studied with its artificial ligands in literature, it is evident that ITE may well be able to also inhibit cell division^[13-15], induce cell differentiation^[3, 7], promote programmed cell death (apoptosis)^[16, 17], and antagonize estrogen^[4, 18] and androgen^[19, 20] signaling systems for efficient cancer intervention. This multiple mechanism based combating capability makes the ITE therapy truly unique, especially in therapeutic intervention of estrogen-dependent breast cancer and androgen-dependent prostate cancer. The multiple assaulting strategies ITE uses in combating cancer make it possible to sustain its therapeutic efficacy (single mechanism based noncytotoxic therapies will lose their efficacies soon after a cancer is no longer dependent on a specific function the therapies target for survival). The sustainability in therapeutic potency makes it possible to eradicate cancer eventually (if a cancer can be inhibited and assaulted for long enough, it will possibly die away entirely). For the obesity therapy, beside choking fat tissues to death, ITE will be efficacious not only because it can inhibit cell division and promote apoptosis but also because it can block the transformation of a normal cell to fat cells^[21-23] and can control food intake and energy balance^[24, 25].

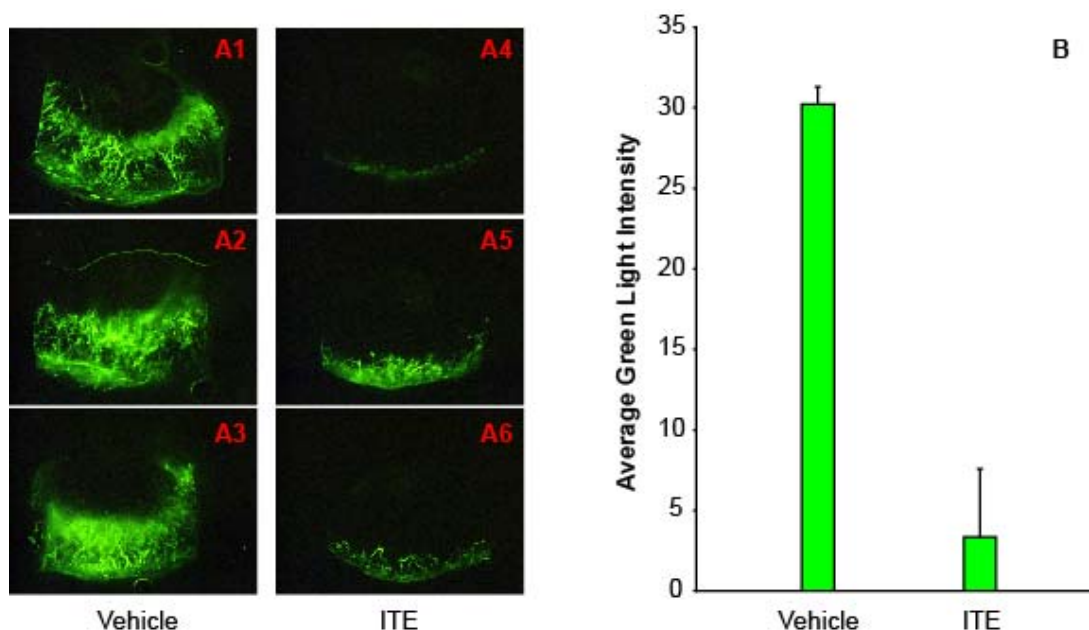


Fig. 4. While i.p. injection of vehicle (DMSO:propylene glycol, 1:1, v/v) did not affect the bFGF induced angiogenesis (A1 to A3), ITE in the vehicle (10 mg/kg bodyweight) inhibited strongly the angiogenesis process (A4 to A6). The quantification (B.) confirms the visual impression. The inhibition is still very effective at a much lower concentration (100 μ g/kg bodyweight, data not shown).

2-4-3. Evidence supporting the efficacy of ITE cancer therapy

Even though most of the artificial ligands for AhR are environmental toxins and thus cannot be used as therapeutic agents, for the purpose of understanding AhR functions, TCDD, 6-methyl-1,3,8-trichlorodibenzofuran (6-MCDF), and 8-methyl-1,3,6-trichlorodibenzofuran (8-MCDF) were used to discover that the Ah receptor was able to inhibit the growth of carcinogen induced rat mammary tumor^[26, 27] and human breast tumor cell (MCF-7) xenograft^[28]. **Fig. 5** represents this type of studies^[27].

2-4-4. Evidence supporting the specificity of ITE cancer therapy

Supporting the possible specificity of ITE therapy, the Ah receptor was reported to be highly expressed in pancreatic cancer tissues from 14 out of 15 patients but faintly expressed in all normal pancreatic tissues examined^[29]. Furthermore, the AhR artificial ligands were shown to be able to inhibit the *in vitro* growth of pancreatic cancer cells expressing the Ah receptor^[29]. Similarly, the enhanced AhR expression is also documented with prostate cancer^[30].

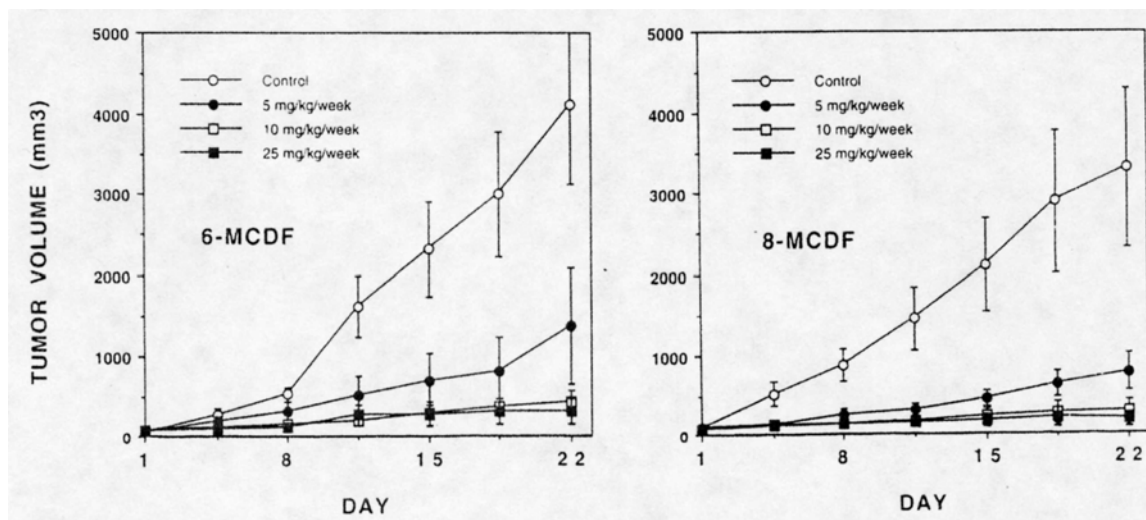


Fig. 5. AhR artificial ligands, 6-MCDF (left) and 8-MCDF(right), inhibit the growth of rat mammary tumor induced by 7,12-dimethylbenz[α]anthracene. Animals were injected i.p. weekly with corn oil as vehicle control or compounds dissolved in the vehicle^[27] (reproduced with permission from Dr. Stephen Safe of Texas A & M University, College Station, TX 77843).

2-4-5. Possibility of low side effect(s) from ITE therapy

With the grand therapeutic opportunity of ITE outlined, we will analyze why we think the ITE hormone therapy may well have low side effect(s). Aspects of metabolism of exogenous chemicals vs. a natural hormone, probability of “off-target” binding and interaction of exogenous chemicals vs. a natural hormone, preliminary observation of ITE dosed animals, and a reported study in ITE biology and toxicology will be analyzed.

2-4-5-1. ITE has a natural and safe way of metabolism

In our body, the metabolism of exogenous chemicals, including most of therapeutic agents used so far for cancer (and other disorders) and those AhR artificial ligands, presents quite a challenge. In an effort to get rid of those exogenous chemicals, many chemically active intermediates or radicals will be produced unavoidably during the metabolic elimination of those chemicals. Those radicals or chemically active intermediates will assault many cellular substances including, but not limited to, nucleic acids (**Fig. 6**, for an example) and proteins, leading to a lot of adverse side-effects including the induction of other types of cancer. Actually, toxicity and side-effects are limiting factors for a lot of therapies for cancer (cytotoxic agents, for example) and other disorders. On the other hand, a simple enzymatic action, without producing any chemically active intermediate, will convert the lipophilic ITE into a polar ITC circulating naturally in the blood (**Fig. 3**). ITC could then be easily excreted, most probably, through the urinary system or further degraded through a natural and safe way of metabolism when its level goes higher. It is, therefore, very clear that it may have a completely different consequence of administering the natural hormone ITE from that of exogenous

chemicals including AhR artificial ligands. Therefore, the concern that most of AhR artificial ligands happen to be environmental toxicants and thus main functions of the Ah receptor seem to “mediate” toxicological responses has also been addressed.

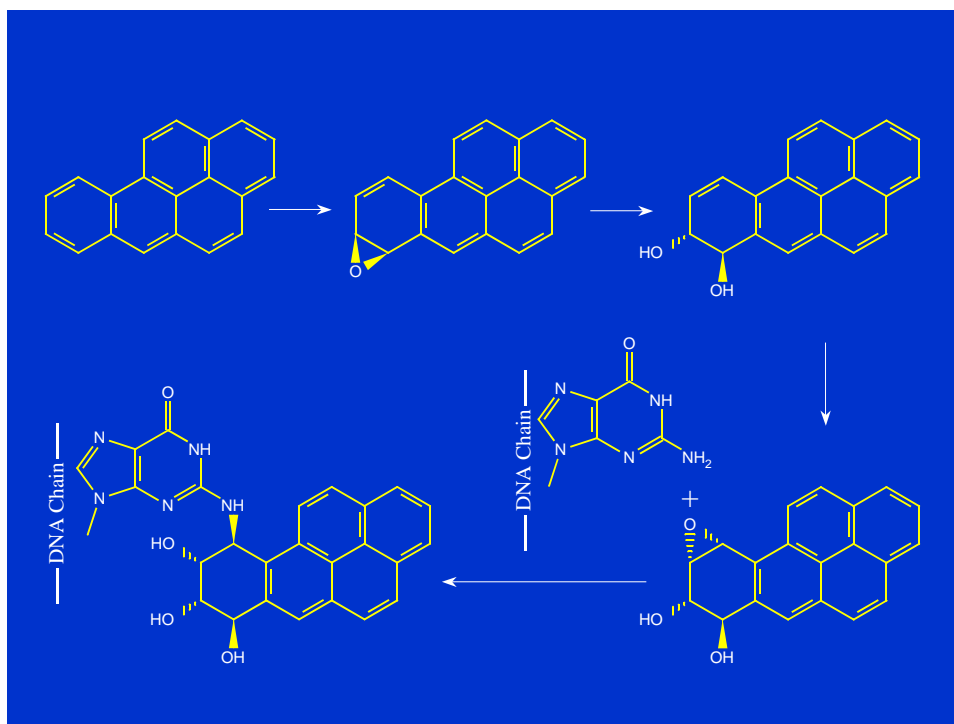


Fig. 6. Some chemically active intermediates from metabolic elimination of exogenous chemicals, including AhR artificial ligands, will attack a base, the genetic signal, on the DNA chain thus destroying or disrupting the flow of genetic information.

2-4-5-2. ITE should have very low chance of “off-target” action

One of the important reasons for current therapeutic agents to be high in side effects is that since they are designed by humans, not the nature, they tend to have very high chance to bind to and interact with other molecules (including proteins and receptors) than their expected targets in the body. These “off-target” bindings and interactions account for significant opportunities for side effects. On the other hand, the binding of the natural hormone to its receptor (the Ah receptor) is very specific and precise since it is designed and manufactured by the nature. The hormone ITE, other than those human designed chemicals, will then have very low chance of binding to and interact with other proteins or molecules to provoke “off-target” problems.

2-4-5-3. No adverse effect of ITE has been observed so far

At least visually, we have not observed any adverse reaction from mice or rats when we were conducting animal experiments with ITE at a concentration of as high as 10 mg/kg bodyweight. The visual impression was supported by a reported study of ITE biology and toxicity together with a toxic AhR artificial ligand, TCDD^[31].

2-5. EASY SYNTHESIS AND ORAL ADMINISTRATION

Since the hormone ITE is a small organic compound with its chemical structure solved by us, it can be easily synthesized on large scale. It can also be easily formulated for oral administration (and other routes, if desired). The oral administration is the most attractive route because of its great convenience and freedom for patients.

3. FURTHER DEVELOPMENT

3-1. THE COMPANY

AhR Pharmaceuticals, Inc., a type C corporation registered in Wisconsin, USA, has been established on October 14, 2005 to develop the hormone ITE and its analogs into potent and sustainable but low side-effect therapeutic agents in combating cancer, obesity, and blinding retinopathy. The company is currently wholly owned by its founder, Dr. Jiasheng (Jason) Song. The company will be governed by its board of directors and managed by its officers.

3-1-1. The board of directors

Dr. Hector F. DeLuca, a co-inventor of the patented technology platform of the company and world authority on vitamin D endocrine system and its therapeutic applications, is agreed to serve on the board of directors of the company. Dr. DeLuca is the President & CEO, Deltanoid Pharmaceuticals, Inc., Madison, Wisconsin, USA; a Professor, Department of Biochemistry, University of Wisconsin-Madison, Madison, Wisconsin, USA; and a member of the National Academy of Science of USA. Dr. Jiasheng (Jason) Song, a long time associate of Dr. DeLuca, co-inventor of the patented technology platform, and the founder of the company, will also serve on the board. Other members of the board, to be named within a year or so, will be selected from leaders in fields of business, finance, marketing, and academic sciences.

3-1-2. The initial management team

The AhR Pharmaceuticals is temporarily managed by its founder, Dr. Jiasheng (Jason) Song, who functions also as the Chief Scientific Officer (CSO) of the company. In assisting the management, Charles E. Neider of Neider & Boucher, a legal service and business consulting firm of Madison, Wisconsin, has been serving as a Legal Advisor and Kevin J. Kelbel of Smith & Gesteland, a public accounting and business consulting firm also of Madison, Wisconsin, an Business Consultant/Accountant.

3-1-2-1. The background information about Jiasheng (Jason) Song

Dr. Jiasheng (Jason) Song received his Ph. D. in Genetics from Kansas State University, Manhattan, Kansas, USA in 1990. Before came here to the United States, he served as a full time faculty member in Shanghai College of Agriculture (part of Shanghai Jiaotong University now), from where he received his BS degree. When in the Department of Biochemistry, University of Wisconsin-Madison, Madison, Wisconsin, USA, Dr. Song, together with Dr. Hector DeLuca, directed and trained several Ph.D. students. He also trained and supervised several technicians, senior undergraduate students (for their theses research), and numerous laboratory assistants in a 10-year endeavor of elucidating the natural hormone (ITE) system. Along with his broad scientific background and expertise not only in the Ah receptor field but also in the fields of biology, biochemistry, pharmacology, genetics, chemistry, and molecular biology, Dr. Song brings to the company also management experience and skills. The scientific credentials and management experience make him well qualified to direct and manage

research and development activities of a science company like AhR Pharmaceuticals, Inc., which is built entirely on a solid foundation of fundamental science and poised to grow rapidly under the guidance of serious science and scientific thinking.

3-1-3. Establishment of a permanent management team

To establish a long-term management team of the company, we are actively engaged in a process of recruiting a qualified business professional to be the President and Chief Executive Officer (CEO). To increase the productivity during the starting up period, the CEO could also serve as the Chief Financial Officer (CFO) of the company.

3-2. THE TECHNOLOGY PLATFORM

The mission of the AhR Pharmaceuticals is to develop the efficacious and sustainable but low side-effect therapies for cancer, obesity, and blinding retinopathy based on a technology platform developed by Dr. Jiasheng (Jason) Song (the founder of the company), Dr. Hector F. Deluca (agreed to serve on the company's board of directors), and their colleagues. The foundation intellectual property of the technology platform includes three issued US patents: US 6,916,834 B2, US 7,002,019 B2, and US 7,419,992 B2 covering, respectively, the therapeutic preparation of ITE, the chemical synthesis of the natural hormone, and the therapeutic intervention in angiogenesis implicated disorders with the hormone. Since Dr. Song and his team were at the University of Wisconsin-Madison when the invention was made, the Wisconsin Alumni Research Foundation (WARF) owns the technology (consisted of these patents). AhR Pharmaceuticals is a licensee of the technology. The natural hormone will potently combat cancer, obesity, and blinding retinopathy through blocking new blood vessel generation, inhibiting cell division, promoting apoptosis (programmed cell death), inducing cell differentiation, antagonizing estrogen and androgen signaling systems, inhibiting the transformation of a normal cell to fat cells, and controlling hypothalamus actions to regulate appetite and energy balance. It is this multiple mechanism based mode of action together with the possibility of low side effect(s) makes the technology platform truly unique and distinctive.

3-3. THE STRATEGY

We will first focus on ITE efficacy on xenograft mouse model for human breast cancer and the other therapies will follow gradually. Pre-clinical studies in pharmacodynamics (PD, efficacies of the hormone), pharmacokinetics (PK), and toxicity/toxicokinetics (TK) of the hormone will be conducted to prepare for the application of IND (Investigational New Drug) and phase I clinical studies. Phase I and/or phase II clinical trials will be conducted thereafter. The company will not produce or sell any pharmaceutical products to end-users in the current business model. Instead, AhR Pharmaceuticals will market its intellectual property and expertise related to specific ITE therapies to other pharmaceutical companies for further down stream development. Therefore, the results of these studies will be announced to the world through high quality academic publication and patent filing. At the same time, certain mature and fully functional pharmaceutical companies will be targeted to market the licenses for specific therapies together with our expertise. In addition to the near term focus, we will also develop and

test analogs of ITE, use the ITC (the major ITE metabolite and precursor) as prodrug, and pursue basic science of the hormone system pertinent to potential elegant drug design and development in a long run.

3-4. THE CURRENT FOCUS

Currently, we are focusing on raising a fund of \$500,000 (up to \$1,000,000) to fund the pre-clinical animal studies to prepare for clinical studies. To reduce the cost (and the risk of our investors therefore) and speed up the process, we are going to contract the initial animal study to a CRO (Contract Research Organization) instead of setting up our own facility and then conducting the experiments. To further reduce the cost (risk), we are exploring an option of contracting the initial study to a carefully selected, high quality CRO in China. Briefly, human cancer tissues or cell lines will be inoculated into those immune compromised mice (so that they will not reject human cancer tissues or cell lines) to establish human cancers on animals. The hormone ITE dissolved in a selected vehicle system will be injected for a month or so. The tumor sizes will be continuously monitored and compared with the ones on those mice injected with the vehicle system alone. Once the efficacy is firmly confirmed, more studies necessary to prepare for clinical trials and to satisfy FDA requirements for IND (Investigational New Drug) application will be designed and conducted.

4. CONTACT INFORMATION

If you are as excited as we are and highly value this investment opportunity in terms of not only high potential return but also high impact you will help to make on public health, please contact Dr. Jiasheng (Jason) Song, the Founder and Chief Scientific Officer (CSO) of the AhR Pharmaceuticals, Inc. by:

Email: jasons@ahrpharma.com

Phone: (608) 692-4791

Fax: (608) 848-2558

5. CITED LITERATURES

1. Schmidt, J.V. and Bradfield, C.A. 1996. Ah receptor signaling pathways. *Annu Rev Cell Dev Biol.* **12**:55-89.
2. Whitlock, J.P.J. 1999. Induction of cytochrome P4501A1. *Ann. Rev. Pharmacol. Toxicol.* **39**:103-125.
3. Poellinger, L. 2000. Mechanistic aspects-the dioxin (aryl hydrocarbon) receptor. *Food Add. Contam.* **17**(4):261-266.
4. Safe, S., and McDougal, A. 2002. Mechanism of action and development of selective aryl hydrocarbon receptor modulators for treatment of hormone-dependent cancers. *Internatl. J. Oncol.* **20**(6):1123-1128.

5. Safe, S., and Wormke, M. 2003. Inhibitory aryl hydrocarbon receptor-estrogen receptor a cross-talk and mechanisms of action. *Chem. Res. Toxicol.* **16**(7):807-816.
6. Walisser, J.A., Bunger, M.K., Glover, E., and Bradfield, C.A. 2004. Gestational exposure of Ahr and Arnt hypomorphs to dioxin rescues vascular development. *Proc. Natl. Acad. Sci. USA.* **101**(47):16677-16682.
7. Puga, A., Tomlinson, C.R., and Xia, Y. 2005. Ah receptor signals cross-talk with multiple developmental pathways. *Biochem. Pharmacol.* **69**(2):199-207.
8. Song, J., Clagett-Dame, M., Peterson, R.E., Hahn, M.E., Westler, W.M., Sicinski, R.R., and DeLuca, H.F. 2002. A ligand from the aryl hydrocarbon receptor isolated from lung. *Proc. Natl. Acad. Sci. USA.* **99**(23):14694-14699.
9. Grzywacz, P., Sicinski, R.R., and DeLuca, H.F. 2003. A concise synthesis of an AHR endogenous ligand with the indolecarbonylthiazole skeleton. *Heterocycles.* **60**(5):1219-1224.
10. Korza, G., and Ozols, J. 1988. Complete covalent structure of 60-kDa esterase isolated from 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced rabbit liver microsomes. *J. Biol. Chem.* **263**(7):3486-3495.
11. Song, J., Clagett-Dame, M., Hahn, M.K., Peterson, R.E., and DeLuca, H.F. 2008. The production and inactivation of an endogenous ligand for the Ah receptor. Manuscript Prepared.
12. Song, J., Barycki, R., Clagett-Dame, M., and DeLuca, H.F. 2008. An enzymatic system converting ITC to ITE, an Ah receptor physiological ligand. Manuscript in Preparation.
13. Elizondo, G., Fernandez-Salguero, P., Sheikh, M.S., Kim, G.Y., Fornace, A.J., Lee, K.S., and Gonzalez, F.J. 2000. Altered cell cycle control at the G(2)/M phases in aryl hydrocarbon receptor-null embryo fibroblast. *Mol. Pharmacol.* **57**(5):1056-1063.
14. Puga, A., Xia, Y., and Elferink, C. 2002. Role of the aryl hydrocarbon receptor in cell cycle regulation. *Chemico-Biol. Interact.* **141**(1-2):117-130.
15. Marlowe, J.L., Knudsen, E.S., Schwemberger, S., and Puga, A. 2004. The aryl hydrocarbon receptor displaces p300 from E2F-dependent promoters and represses S phase-specific gene expression. *J. Biol. Chem.* **279**(28):29013-29022.
16. Kramer, H.J., Podobinska, M., Bartsch, A., Battmann, A., Thoma, W., Bernd, A., Kummer, W., Irlinger, B., Steglich, W., and Mayser, P. 2005. Malassezin, a novel agonist of the aryl hydrocarbon receptor from the yeast *Malassezia furfur*, induces apoptosis in primary human melanocytes. *Chembiochem.* **6**(5):860-865.
17. Park, K.T., Mitchell, K.A., Huang, G.M., and Elferink, C.J. 2005. The aryl hydrocarbon receptor predisposes hepatocytes to Fas-mediated apoptosis. *Mol. Pharmacol.* **67**(3):612-622.
18. Oenga, G.N., Spink, D.C., and Carpenter, D.O. 2004. TCDD and PCBs inhibit breast cancer cell proliferation *in vitro*. *Toxicol. in vitro.* **18**(6):811-819.
19. Jana, N.R., Sarkar, S., Ishizuka, M., Yonemoto, J., Tohyama, C., and Sone, H. 1999. Cross-talk between 2,3,7,8-tetrachlorodibenzo-p-dioxin and testosterone signal transduction pathways in LNCaP prostate cancer cells *Biochem. Biophys. Res. Comm.* **256**(3):462-468.

20. Morrow, D., Qin, C.H., Smith, R., and Safe, S. 2004. Aryl hydrocarbon receptor-mediated inhibition of LNCaP prostate cancer cell growth and hormone-induced transactivation. *J. Ster. Biochem. Mol. Biol.* **88**(1):27-36.
21. Shimba, S., Wada, T., and Tezuka, M. 2001. Arylhydrocarbon receptor (AhR) is involved in negative regulation of adipose differentiation in 3T3-L1 cells: AhR inhibits adipose differentiation independently of dioxin. *J. Cell Sci.* **114**(15):2809-2817.
22. Hanlon, P.R., Ganem, L.G., Cho, Y.C. Yamamoto, M., and Jefcoate, C.R. 2003. AhR- and ERK-dependent pathways function synergistically to mediate 2,3,7,8-tetrachlorodibenzo-p-dioxin suppression of peroxisome proliferator-activated receptor-gamma 1 expression and subsequent adipocyte differentiation. *Toxicol. Appl. Pharmacol.* **189**(1):11-27.
23. Hanlon, P.R., Cimafranca, M.A., Liu, X.Q., Cho, Y.C., and Jefcoate, C.R. 2005. Microarray analysis of early adipogenesis in C(3)H10T1/2 cells: Cooperative inhibitory effects of growth factors and 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Toxicol. Appl. Pharmacol.* **207**(1):39-58.
24. Fetissov, S.O., Huang, P., Zhang, Q., Mimura, J., Fujii-Kuriyama, Y., Rannug, A., Hokfelt, T., and Ceccatelli, S. 2004. Expression of hypothalamic neuropeptides after acute TCDD treatment and distribution of Ah receptor repressor. *Reg. Peptides.* **119**(1-2):113-124.
25. Yang, C., Boucher, F., Tremblay, A., and Michaud, J.L. 2004. Regulatory interaction between arylhydrocarbon receptor and SIM1, two basic helix-loop-helix PAS proteins involved in the control of food intake. *J. Biol. Chem.* **279**(10):9306-9312.
26. Holcomb, M., and Safe, S. 1994. Inhibition of 7,12-dimethylbenz[a]anthracene-induced rat mammary tumor growth by 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Cancer Let.* **82**:43-47.
27. McDougal, A., Wilson, C., and Safe, S. 1997. Inhibition of 7,12-dimethylbenz[a]anthracene-induced rat mammary tumor growth by aryl hydrocarbon receptor agonists. *Cancer Let.* **120**:53-63.
28. Gierthy, J.F., Bennett, J.A., Bradly, L.M., and Cutler, D.S. 1993. Correlation of in vitro and in vivo growth suppression of MCF-7 human breast cancer by 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Cancer Res.* **53**:3149-3153.
29. Koliopanos, A., Kleeff, J., Xiao, Y., Safe, S., Zimmermann, A., Buchler, M. W., and Friess, H. 2002. Increased arylhydrocarbon receptor expression offers a potential therapeutic target for pancreatic cancer. *Oncogene.* **21**:6059-6070.
30. Kashani, M., Steiner, G., Haitel, A., Schaufler, K., Thalhammer, T., Amann, G., Kramer, G., Marberger, M., and Scholler, A. 1998. Expression of the aryl hydrocarbon receptor (AhR) and the aryl hydrocarbon receptor nuclear translocator (ARNT) in fetal, benign hyperplastic, and malignant prostate. *Prostate.* **37**(2):98-108.
31. Henry, E.C., Bemis, J.C., Henry, O., Kende, A.S., and Gasiewicz, T.A. 2006. A potential endogenous ligand for the aryl hydrocarbon receptor has potent agonist activity in vitro and in vivo. *Arch Biochem Biophys.* **450**(1):67-77.