

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/362623803>

Development and Challenges of Synthetic Retinoid Formulations in Cancer

Article in *Current Drug Delivery* · August 2022

DOI: 10.2174/1567201819666220810094708

CITATIONS

5

READS

130

6 authors, including:



Sara Assi

American University of Beirut

1 PUBLICATION 5 CITATIONS

SEE PROFILE



Hiba El Hajj

American University of Beirut

108 PUBLICATIONS 3,139 CITATIONS

SEE PROFILE



Berthe Hayar

American University of Beirut

10 PUBLICATIONS 54 CITATIONS

SEE PROFILE



Claudio Pisano

Medicinal Investigational Research, BIOGEM SCARL

230 PUBLICATIONS 7,225 CITATIONS

SEE PROFILE

REVIEW ARTICLE

Development and Challenges of Synthetic Retinoid Formulations in Cancer

Sara Assi¹, Hiba El Hajj², Berthe Hayar³, Claudio Pisano⁴, Walid Saad^{5,*} and Nadine Darwiche^{3,*}

¹Department of Biomedical Engineering, Maroun Semaan Faculty of Engineering and Architecture, American University of Beirut, Beirut, Lebanon; ²Department of Experimental Pathology, Immunology and Microbiology, Faculty of Medicine, American University of Beirut, Beirut, Lebanon; ³Department of Biochemistry and Molecular Genetics, Faculty of Medicine, American University of Beirut, Beirut, Lebanon; ⁴Biogem, Institute of Molecular Biology and Genetics, via Camporeale, 83031 Ariano Irpino(AV), Italy; ⁵Department of Chemical Engineering, Maroun Semaan Faculty of Engineering and Architecture, American University of Beirut, Beirut, Lebanon

ARTICLE HISTORY

Received: March 21, 2022
Revised: April 08, 2022
Accepted: May 04, 2022

DOI:
10.2174/1567201819666220810094708

Abstract: Retinoids represent a class of chemical compounds derived from or structurally and functionally related to vitamin A. Retinoids play crucial roles in regulating a range of crucial biological processes spanning embryonic development to adult life. These include regulation of cell proliferation, differentiation, and cell death. Due to their promising characteristics, retinoids emerged as potent anti-cancer agents, and their effects were validated *in vitro* and *in vivo* preclinical models of several solid and hematological malignancies. However, their clinical translation remained limited due to poor water solubility, photosensitivity, short half-life, and toxicity. The development of retinoid delivery formulations was extensively studied to overcome these limitations. This review will summarize some preclinical and commercial synthetic retinoids in cancer and discuss their different delivery systems.

Keywords: Synthetic retinoid, delivery system, formulation, development, drug, cancer.

1. INTRODUCTION

Retinoids are a set of signaling molecules comprising both natural and synthetic derivatives of vitamin A. These compounds play critical roles in embryonic development, adult physiology, vision, cell proliferation, cell differentiation, reproduction, and immune and neural functions [1]. Accordingly, retinoids target several diseases, particularly cancer [2, 3]. The chemical structure of vitamin A was first described in 1931. It consists of cyclic hydrophobic and polar groups separated by a central polyene [4].

Naturally occurring retinoids comprise vitamin A (retinol), retinal, and retinoic acid (RA) [5]. The most common types of RA include all-*trans* RA (ATRA, also named tretinoin), 9-*cis* RA (alitretinoin), and 13-*cis* RA (isotretinoin) [6-8]. These forms play major roles in cell growth, differentiation, and death [9]. However, poor water solubility, bioavailability, photosensitivity, short half-life, and toxicity were

documented [10, 11]. Hence, synthetic retinoids were developed to overcome these disadvantages and increase the chemotherapeutic ability of natural retinoids [12]. The first generation of the synthetic derivatives of the RA isomers is tretinoin, alitretinoin, and isotretinoin [7, 8]. Other synthetic derivatives (etretinate and its metabolite acitretin) belong to the second generation. The third generation (bexarotene, adapalene, and tazarotene) and fourth generation (seletinoid G) of retinoids were also synthesized [13]. Other commonly developed synthetic retinoids include N-4-hydroxyphenyl retinamide (HPR, fenretinide) and the adamantyl retinoids CD437 and ST1926, among others [14, 15].

In addition to multiple biological activities, retinoids emerged as potential therapeutic targets in the treatment of cancer. This was mainly due to the documented deregulated retinoid signaling in tumorigenesis [12]. Indeed, retinoids target tumor growth *via* inhibition of proliferation, induction of differentiation, and apoptosis [16]. RA exhibited a distinct role as an anti-cancer agent [17]. ATRA was approved by the Food and Drug Administration (FDA, USA) to treat and manage acute promyelocytic leukemia (APL) [18]. However, the poor aqueous solubility, photosensitivity [11], and reduced half-life [10] of ATRA has limited its success as a single drug in clinical therapy. Hence, new synthetic retinoids with reduced toxicity were generated [19]. The problem of solubility, bioavailability and appropriate targeting of

*Address correspondence to these authors at the Department of Biochemistry and Molecular Genetics, Faculty of Medicine, American University of Beirut, P.O. Box 11-0236, Riyad El-Solh 1107-2020, Beirut/Lebanon; Tel: +961-3-860548; E-mail: nd03@aub.edu.lb and Department of Chemical and Petroleum Engineering, Maroun Semaan Faculty of Engineering and Architecture, American University of Beirut, P.O. Box 11-0236, Riyad El-Solh 1107-2020 Beirut, Lebanon; Tel: +961-3-250922; E-mail: ws20@aub.edu.lb

cells of interest was addressed through developing a range of retinoid delivery formulations based on various systems, including gels, liposomes, and nanoparticles (NPs) [20, 21]. Recently, Ferreira *et al.* reviewed retinoid delivery systems, particularly natural retinoids, in regenerative and therapeutic medicine [21]. This review will focus on the application and challenges of synthetic retinoid formulations in various cancer types.

1.1. Mechanism of Action of Retinoids

Retinoids are lipophilic compounds that need specialized proteins for transport and metabolism [22]. The main blood-circulating retinoid in mammals is retinol, which is transported to cells by binding to retinol-binding protein (RBP). The plasma membrane transporter and receptor STRA6 mediates the uptake of the RBP-retinol complex to the cytosol, where retinol binds to cytosolic retinol-binding protein (CRBP) [23]. Retinol is then converted to ATRA in a two-step enzymatic process: retinol is first oxidized to retinaldehyde which is then oxidized to ATRA. In the cytoplasm, ATRA binds to the cytosolic retinoic acid binding protein (CRABP). Two subtypes exist for both groups of proteins: CRBP I and II and CRABP I and II. There are two families of retinoid nuclear receptors; the RA receptors (RAR) and the retinoid X receptors (RXR), and each family is composed of α , β , and γ isoforms [24]. RARs bind to both ATRA and 9-*cis* RA, while RXRs bind only to 9-*cis*-RA. In addition, RARs and RXRs can form heterodimers with each other.

RXRs can heterodimerize with various receptor families, including thyroid hormone receptor, dihydroxy vitamin D3 receptor (VDR), androgen receptor, fatty acid receptors, liver X receptors (LXR), and peroxisome proliferator-activated receptors (PPARs) [25]. RAR-RXR heterodimers bind to DNA sequences, called the retinoic acid response element [26], promoting the transcription of target genes responsible for modulating cell growth and differentiation [27]. Homodimers of RXRs [28] can also facilitate gene transcription.

1.2. Synthetic Retinoids

Natural retinoids are under intense investigation to enhance their efficacy and reduce toxicity. RA administration is challenging due to its poor solubility (0.21 μM under physiological conditions) in aqueous media [11]. Additionally, RA has a limited circulation time in plasma [10] which hinders its use in various biomedical applications. Tumors acquire resistance to natural retinoids, pressing the need for synthetic analogs that may work through retinoid-receptor-dependent or independent pathways [29]. Over the past decade, efforts have been made to develop less toxic, highly stable, and selective synthetic retinoids [12]. We will focus our review on commonly studied and tested synthetic retinoids in cancer, namely fenretinide, bexarotene, ST1926, and tamibarotene (Fig. 1). While various side effects also limit synthetic retinoids, different drug delivery systems, including liposomes, NPs, micelles, and microparticles, have been examined.

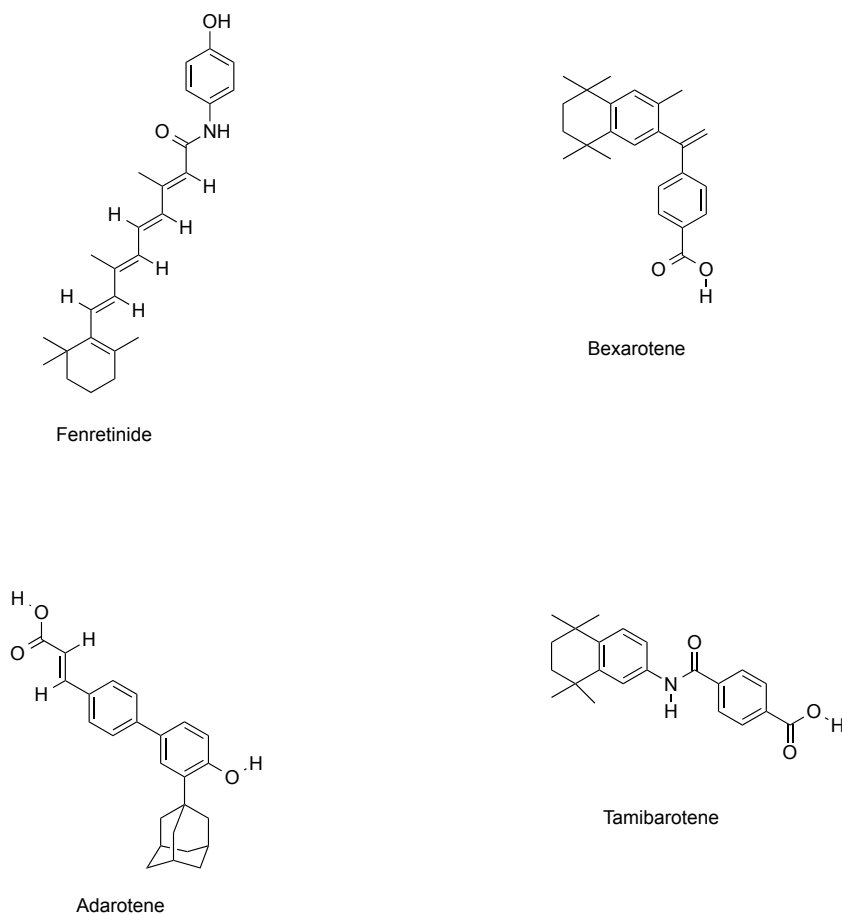


Fig. (1). Chemical Structures of Synthetic retinoids: fenretinide, bexarotene, ST1926, and tamibarotene.

Table 1. Synthetic retinoids in cancer clinical trials and the clinic.

Synthetic Retinoid	Activity	Therapeutic Potential	Clinical Trial Identifier
Fenretinide	Atypical retinoid	Peripheral T-cell lymphoma	NCT02495415
		Relapsed malignancies	NCT01553071
		Breast cancer	NCT01479192
		Bladder cancer	NCT00004154
		Cervical neoplasia	NCT00003075
Bexarotene	Pan agonist	Cutaneous T-cell lymphomas	FDA approved since 1990
Tamibarotene (Am80)	RAR α agonist	Relapsed acute myeloid leukemia/ Relapsed myelodysplastic syndrome	NCT02807558
		Advanced non-small cell lung cancer	NCT01337154
Palovarotene	RAR γ agonist	Multiple osteochondromas	NCT03442985
Trifarotene	RAR γ agonist	Early cutaneous T-cell lymphoma	NCT01804335
AGN194204	RXR agonist	Prostate cancer	NCT01540071
UAB30/9-cis-UAB30	RXR agonist	Nonmelanoma skin cancer	NCT03327064

1.3. Clinical Synthetic Retinoids in Cancer

Synthetic retinoid molecules such as bexarotene have been FDA approved for therapy, while other synthetic retinoids, including fenretinide, tamibarotene, palovarotene, trifarotene, AGN194204, and UAB30/9-cis-UAB30 are currently being studied in clinical trials (Table 1). Fenretinide was examined in many clinical trials and appeared to have a distinct role in the chemoprevention of different types of cancers in humans. Bexarotene is a pan retinoid RXR agonist that has been FDA approved for treating cutaneous T cell lymphoma. Tamibarotene is a selective RAR α agonist approved for relapsed APL in Japan and is still undergoing clinical trials in the United States. Palovarotene was synthesized as a RAR γ agonist and is currently in clinical trials. Trifarotene is a new molecule with selectivity toward the RAR γ agonist. It was FDA-approved for treating acne vulgaris in patients [30]. AGN194204, an RXR-selective retinoid (rexinoid), was studied in clinical trials for the slowing down of resistant prostate cancer, while UAB30 is currently examined in clinical trials for nonmelanoma skin cancers.

2. SYNTHETIC RETINOIDS DELIVERY SYSTEMS FOR CANCER TREATMENT

2.1. Fenretinide

Fenretinide (N-(4-hydroxyphenyl)retinamide; HPR) is a synthetic analogue of ATRA produced in the 1960s [14]. Substituting the carboxyl group of ATRA with an amide-linked-4-hydroxyphenyl group in fenretinide had remarkably reduced side effects and increased anti-cancer efficacy compared to ATRA. Indeed, fenretinide exhibited *in vitro* cytotoxic efficacy against various cancer cells, including neuroblastoma [31], colon cancer [32], liver cancer [33], breast cancer [34], T cell lymphoma, and ovarian cancer [35]. In animal models, fenretinide showed anti-tumor activity in endometrial cancer [36] and AML [37]. This potency made

fenretinide one of the most studied synthetic retinoids in clinical trials [38, 39]. Yet, results were disappointing since the therapeutic plasma levels of fenretinide were not achieved due to its low water solubility and poor bioavailability in some clinical trials [40, 41].

2.1.1. Fenretinide Delivery Systems

Considerable efforts were put into developing fenretinide formulations to enhance its water solubility and bioavailability. Various formulation techniques were investigated, including polymeric micelles [42], ion-pairing [43], and amorphous solid dispersion. Polymeric micelles are characterized by a core-shell structure where the inner core is hydrophobic and the outer shell is hydrophilic [44]. They are widely used as drug delivery systems because of their relatively high stability in circulation, low toxicity, and high efficacy in entrapping hydrophobic compounds [45]. The outer shell of the micelle can prevent reticuloendothelial system (RES) uptake and hydrophobic core aggregation. These micellar characteristics are favorable for passive delivery [46] and drug release at the tumor site by enhanced permeability and retention (EPR) effects [47]. Poly (ethylene glycol) (PEG) is the most commonly used hydrophilic component of micelles due to its biocompatibility, solubilizing potential for hydrophobic drugs, and ability to extend the carrier circulation time *in vivo* [48]. Wang *et al.* prepared a novel self-assembled pro-drug conjugate by esterifying HPR with methoxy polyethylene glycol carboxylic acid (mPEG_{2K}-COOH) to increase the HPR aqueous solubility [42]. The cytotoxicity of fenretinide in HPR-PEG_{2K} conjugates was enhanced towards ovarian and breast cancer cell lines compared to the free retinoid form. Additionally, tumor growth was significantly reduced in xenograft mice bearing ovarian cancer treated with the conjugate micelles compared to those treated with the free drug [42]. The HPR-PEG_{2K} conjugate micelles demonstrated potent anti-tumor activity with nominal toxicity *in vivo*. This may be due to the effects of PEGylation strategies which

extended the blood circulation time, increased the accumulation in tumor sites [49], and the EPR effect [50].

A novel nano-formulation of fenretinide, referred to as “bionanofenretinide (Bio-nFER), was developed to increase the drug aqueous solubility. This formulation is based on an ion pairing approach between fenretinide and phosphatidylcholine, resulting in a micellar system comprised of a fenretinide inner core and a hydrophilic shell formed by phospholipid molecules [43]. The activity of the Bio-nFER formulation was examined both *in vitro* and *in vivo* and was compared to a standard fenretinide formulation [51]. Bio-nFER demonstrated potent cytotoxic activity against cancer stem cells of primary melanoma, glioblastoma, lung, and colon *in vitro* compared to the standard formulation. In addition, cancer stem cells derived from different tumors such as lung, melanoma, and colon xenografts showed a notable decline in tumor growth when treated with Bio-nFER compared to the control group. Importantly, negligible toxicity was observed in mice. This increased anti-tumor efficacy of Bio-nFER *in vitro* and *in vivo* is due to its improved bioavailability, resulting in higher drug exposure at the tumor site [43].

Amorphous solid dispersions (ASD) is a formulation strategy used to enhance the solubility and bioavailability of active pharmaceutical ingredients. ASD can form supersaturated aqueous drug concentrations compared to the crystalline forms of drugs [52]. Many solubility-enhancing excipients were studied, such as polyvinylpyrrolidone (PVP). PVP is one of the most common solubility excipients due to its ability to dissolve in a wide range of solvents [53]. ASD of poorly soluble drugs with PVP has been shown to enhance their solubility [54]. PVP-fenretinide solid dispersion tablets for oral administration were developed to enhance its bioavailability [55]. Poly lactic-co-glycolic acid (PLGA) microsphere formulation of fenretinide showed promising results, which encouraged further development [56]. However, the bioavailability of fenretinide was hindered by drug crystallization. As such, Nieto *et al.* prepared PVP-HPR ASD, where the solubility of fenretinide was significantly enhanced. PVP-HPR ASDs were then loaded into PLGA milli cylinders for controlled release of fenretinide *in vitro* and *in vivo* [57]. The PLGA implants allow local and long-term therapeutics release, permitting therapeutic levels at the target site *in vivo*. The addition of the plasticizer triethyl-o-acetyl-citrate (TEAC) into the PVP-4HPR PLGA implants showed an increase in the release of drug in comparison to the free implants *in vitro* [57]. Further study of the local delivery of PVP-4HPR from PLGA implants will be needed to examine the chemoprevention ability in rodent oral cancer models in the future. All in all, the following studies suggest the need for further examination of improved fenretinide formulations to improve clinical outcomes.

Additionally, there is a need for novel, effective, and safe pharmacological strategies to prevent the development of breast cancer. As such, a phosphatidylcholine-based non-aqueous microemulsion (ME) delivery system capable of phase transformation and gelling in the mammary tissue to prolong the release of fenretinide has been developed [58]. Upon incorporation in water, the ME underwent phase transformation and slowly released fenretinide *in vitro*, possibly

due to the high affinity of fenretinide to the formulation. In line with the slow release of fenretinide, the ME formed a local depot in cell cultures and increased the IC₅₀ values in breast cancer cell lines compared to the free drug solution. The ME formulation reduced cell migration and spheroid viability *in vitro*, despite the increased reported IC₅₀ values. The efficiency of the formulation was then evaluated in -nitrous-N-methyl urea (NMU) induced carcinogenic animal models. The results revealed a significant reduction in the incidence of tumors in rats upon treatment with fenretinide ME compared to other rat groups. The reduction in the incidence of tumors is reported without altering the breast tissue architecture in proximity to the injection site, which indicates that the breast tissue site around the administration is conserved. No local irritation or changes in the leukocyte count were reported, indicating the safety of the proposed fenretinide ME formulation. Additionally, levels of collagen type III were increased in rats treated with fenretinide ME compared to other groups, which indicates that the ME formulation limits the spread and development of the disease [58].

Fenretinide formulations were also investigated in clinical trials. A novel lipid matrix, called LYM-X-SORB™ (LXS), was used to formulate fenretinide, increasing its bioavailability and plasma level concentrations [59, 60]. Fenretinide/LXS oral powder is currently being examined in clinical trials for recurrent ovarian cancers, solid tumors and lymphomas (NCT01535157, NCT00589381). Additionally, an intravenous lipid emulsion formulation of fenretinide was developed using a mixture of egg phospholipids, glycerin, alcohol, and soybean oil [61] and was recently evaluated in a phase I study [38]. This research was performed to determine the safety profile, maximum tolerated dose, pharmacokinetic parameters, and initial anti-tumor activity of fenretinide in patients with malignant tumors. Fenretinide emulsion in adult subjects showed a compliant safety profile and resulted in higher plasma concentrations of fenretinide compared to previous capsule formulations [38]. While single administration of fenretinide exhibited minimal activity in this cohort study, further development of fenretinide emulsion and examining its effect with synergistic agents could improve clinical outcomes.

2.1.2. Fenretinide Delivery Systems in Combination Therapy

Drug combination therapy is a highly promising approach to cancer treatment [62]. Therefore, the co-administration of two or more anti-tumor drugs can display synergistic effects, better tolerability, improved therapeutic effect, decreased side effects and reduced resistance rates.

Retinoids trigger immunogenic cell death and sensitize breast and ovarian cancer cells to death following induction by drugs such as paclitaxel (PTX) [63]. PTX acts by stabilizing microtubules and reducing their dynamic nature, causing a mitotic arrest [64]. However, the clinical application of PTX formulated as Taxol® is limited due to its low aqueous solubility, severe toxicity, and chemoresistance [65]. The combination of fenretinide and PTX is an effective strategy for controlling the growth of glioblastoma cell lines [66]. A nano-drug delivery system was developed for the coadministration of fenretinide and PTX using two biocompatible copolymers of the polyvinyl caprolactam-polyvinyl acetate-

polyethylene glycol graft copolymer (Soluplus[®]) and D-tocopheryl polyethylene glycol 1000 succinate (TPGS) as vehicles. The TGPS-Soluplus[®] mixed micelles represent promising drug delivery systems for cancer treatment [67]. These polymers can form micelles with a low critical micellar concentration and improve the bioavailability and anti-tumor activity of PTX *in vitro* and *in vivo* [68]. A recent study has examined the anti-tumor activity of co-administering fenretinide and PTX using the TGPS-Soluplus[®] as vehicles in ovarian cancer models. The anti-tumor activity was enhanced in ovarian cancer cells treated with mixed polymeric micelles loaded with PTX and fenretinide compared to the free drug groups *in vitro*. Additionally, the tumor growth was significantly inhibited in mice bearing ovarian cancer xenografts injected with mixed polymeric micelles loaded with PTX and fenretinide in comparison to the free combination drug group [69].

Nanoencapsulation of fenretinide in various drug delivery systems increased drug solubility, bioavailability, and permeability at tumor sites [43, 70], as mentioned previously. Fenretinide encapsulation in combination with anti-tumor drugs might pave the way for novel therapeutic systems that can generate successful therapeutic outcomes *in vivo*, bypassing the need for single drug therapies and their related side effects. For instance, nano micelles containing fenretinide combined with lenalidomide were developed to examine their anti-tumor activity in a neuroblastoma model. Lenalidomide is the standard treatment regimen for multiple myeloma and other types of cancer [71-73]. It was chosen as a combinatory drug with fenretinide due to its anti-angiogenic properties and favorable toxicity profile. While the anti-angiogenic effects of lenalidomide were not examined in neuroblastoma models, it remains a promising drug due to its effect on enhancing the activation and overcoming the suppression of natural killer cells in the neuroblastoma milieu [74]. The nanomicelles containing fenretinide and the lenalidomide combination demonstrated a significant anti-tumor effect compared to the nanomicelles containing fenretinide alone *in vivo*. This observed enhanced anti-tumor effect is attributed to the antiangiogenic outcome of lenalidomide and the cytotoxic properties of fenretinide in tumor cells [75].

2.2. Retinoid Bexarotene

Bexarotene, sold under the brand Targretin, is an RXR agonist which selectively activates all three RXR subtypes [76]. Bexarotene plays an important role in regulating gene expression, modulating cell growth, activating cell apoptosis, and regulating tumor development [77, 78]. It was FDA approved to treat cutaneous T-cell lymphoma [79]. Additionally, it exhibited promising anticancer activity against AML [80], non-small cell lung cancer (NSCLC) [76], and breast cancer [81]. However, the clinical utilization of bexarotene is limited due to its limited water solubility and slow dissolution behavior, leading to poor drug bioavailability. Oral administration of bexarotene can cause adverse side effects, including hypothyroidism and hypertriglyceridemia [82].

2.2.1. Bexarotene Delivery Systems

Various strategies were developed to increase the bioavailability of bexarotene, including albumin-based drug delivery systems [83] and mesoporous silica systems [84]. Ad-

ditionally, nanocrystals emerged in the early nineties as a new drug delivery system to enhance oral bioavailability and overcome the solubility issue for many drugs [85], including bexarotene [86]. Nanocrystals are solid nanosized drug particles, stabilized either by surfactants, polymers or both [87]. Since the surface area of the nanocrystals is enlarged, the dissolution velocity and saturation velocity are increased, thus improving the bioavailability of poorly water-soluble drugs. The FDA has approved many nanocrystal drug products since 1995 for several indications, and other products are still in clinical trials [88]. Chen *et al.* were the first group to prepare bexarotene nanocrystals for oral and parenteral application [89]. The saturation solubility and dissolution rate of the bexarotene nanocrystals were significantly improved compared to bexarotene alone in the *in vitro* studies. The *in vivo* pharmacokinetic studies were carried out in rats and showed that the bexarotene nanocrystals increased the bioavailability of bexarotene compared to the drug alone after oral and intravenous administration [89]. Moreover, bexarotene nanocrystals were prepared as a drug delivery system for the treatment of lung cancer. The retention time of the drug was amplified in mice treated with bexarotene nanocrystals compared to those treated with free bexarotene after oral administration. As such, the efficacy and durability of the drug in the lung increased, and the cardiac toxicity decreased. Additionally, the biodistribution of bexarotene became modified, resulting in higher *in vivo* bioavailability in both the blood and the lung. The anti-tumor activity of bexarotene nanocrystals was enhanced compared to bexarotene alone in xenograft animal models. Bexarotene nanocrystals serve as a promising formulation for the treatment of lung cancer [90].

The preparation of amphiphilic prodrugs as a formulation strategy gained much attention recently. Conjugation of a hydrophobic drug to hydrophilic segment results in an amphiphilic prodrug that can assemble into NPs [91]. Dual bexarotene-tailed phospholipid (DBTP) conjugate-based nanovesicles were shown to be internalized by cancer cells and release bexarotene. Additionally, the bexarotene DBTP nanoconjugates demonstrated higher anti-tumor activity against several cancer cells *in vitro* compared to free bexarotene, providing the potential for further development of the formulation [92].

The administration of oral bexarotene is limited by side effects of hypothyroidism and hypertriglyceridemia, which is, in turn, associated with atherosclerosis increasing the risk for cardiovascular diseases. Therefore, formulation strategies are needed to minimize the side effects of administering bexarotene orally. Aerosol bexarotene formulation demonstrated strong chemopreventive activity against subtypes of lung cancer, squamous cell carcinoma, and adenocarcinoma *in vivo* models. The plasma triglycerides and cholesterol levels were not increased due to the new formulation, and no toxicity was observed [93]. In summary, the aerosol administration of bexarotene provides favorable outcomes compared to its oral administration, which could have potential in future clinical trials.

2.3. Atypical Adamantyl Retinoid ST1926

ST1926, known as Adarotene, is a synthetic adamantyl retinoid that belongs to the class of atypical retinoids. It was

developed as a 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437) analog and demonstrated to be stable and orally bioavailable [94]. ST1926 demonstrated anti-cancer activities against various tumor models including AML [95], neuroblastoma [96], rhabdomyosarcoma [97], ovarian cancer [98], adult T cell leukemia [99], chronic myeloid leukemia [100], primary effusion lymphoma [101], breast cancer [102], and prostate cancer [103]. Moreover, ST1926 inhibited the proliferation of human colorectal cancer cells *in vitro* and reduced tumor progression in xenograft colorectal cancer mouse models [104]. Importantly, ST1926 inhibited the growth of various ATRA-resistant AML cell lines and primary AML patients-derived blasts, prolonged survival and reduced tumor burden in AML xenograft mice. Due to its promising properties, ST1926 entered phase I clinical trials for patients with ovarian cancer [105]. However, ST1926 clinical development was hindered since it underwent rapid glucuroconjugation, significantly reducing its bioavailability [106].

2.3.1. ST1926 Delivery Systems

The main approach studied so far to improve the bioavailability of ST1926 is by formulating it into NPs [107]. Nanomedicine has gained significant interest over the years as it provides effective drug delivery, enhanced stability, bioavailability, and permeability, thereby minimizing drug dosage and toxicity [108]. The use of NP formulations in drug delivery has been applied in various cancer models and was demonstrated to advance the ability of drugs to reach specifically targeted sites in a controlled manner. The FDA has approved several NP formulations that are currently used in the clinic [109], including Doxil, which is used to treat ovarian cancer and Kaposi's sarcoma [110], and Abraxane, which is used to treat NSCLC, and pancreatic cancer [111, 112]. PLGA-based NPs were efficient in delivering ATRA in AML cells [113]. In addition to AML cells, this latter formulation improved ATRA's anti-cancer activity and bioavailability in comparison to its free form in liver carcinoma *in vitro* and *in vivo* [114]. We studied the preclinical efficacy of ST1926-NP in AML *in vitro* and *in vivo* models [107]. ST1926-NP significantly improved survival and reduced tumor burden in AML xenografted mice. Noteworthy, ST1926-NP prolonged survival of AML xenografted mice at four-fold lower concentrations than the free retinoid form without detecting any toxicity [107]. Further development of this formulation might pave the way for its use in the clinic.

2.4. Tamibarotene

Tamibarotene (formerly referred to as Am80) is a selective RAR α agonist, synthesized in 1984 and approved for APL treatment in Japan [115]. Tamibarotene was developed to overcome ATRA resistance due to its selectivity as a RAR α agonist, unlike ATRA, which also binds to RAR β and RAR γ [116]. As such, the administration of tamibarotene is likely to result in fewer side effects than ATRA. Tamibarotene is more potent than ATRA in inducing *in vitro* differentiation in human leukemic cell lines [117]. Additionally, tamibarotene may achieve higher plasma concentrations than ATRA since it has a low affinity for CRABP, making it an effective treatment in patients with ATRA-resistant APL [118]. Tamibarotene showed beneficial effects over ATRA in a maintenance therapy study of patients newly diagnosed

with APL [119]. It has also demonstrated efficacy in treating hepatocellular carcinoma [120, 121]. However, when orally administered, tamibarotene is limited by its poor solubility and absorption, and as such, it has low bioavailability. Therefore, formulation strategies are being examined to improve its bioavailability for further clinical development [122].

2.4.1. Tamibarotene Delivery Systems

Microspheres were used to improve the solubility of tamibarotene [120]. Microspheres are a common controlled drug delivery system that releases drugs slowly at the desired rate. They can encapsulate different drugs released by different mechanisms such as dissolution, osmotic pressure, and degradation [123]. This strategy is useful in improving the efficacy of drugs and reducing their related side effects. PLGA is the most widely used carrier for microencapsulation and delivery of drugs. It is a synthetic copolymer containing both lactic acid and glycolic acid. By tuning the ratio of lactic acid to glycolic acid, the degradation time can be tailor-made to match that of the tissue regeneration timeframe. PLGA microspheres have received significant attention lately due to their biocompatibility and biodegradability. Tamibarotene-loaded PLGA microspheres for intratumoral injections were developed by the emulsion solvent evaporation method, and their anti-tumor activity was examined in a hepatocellular carcinoma model [120]. The newly developed formulation had favorable characteristics such as high encapsulation efficiency, drug loading capacity, and uniform distribution and size. For the pharmacokinetics study, mice injected with tamibarotene-loaded PLGA microspheres had a higher drug concentration in the tumor site than those injected with free tamibarotene. This implies that the encapsulation of tamibarotene into microspheres can prolong the retention time of the drug in tumors and improve the therapeutic outcome. Moreover, the pharmacodynamics studies showed that tamibarotene-loaded PLGA microspheres had a sustained inhibitory effect on the growth of tumors, increasing the efficacy of tamibarotene [120]. The different synthetic retinoid formulations discussed are summarized in Fig. (2) and Table 2.

3. CHALLENGES AND PERSPECTIVES

The clinical translation of synthetic retinoid formulations is low despite extensive investigations of several drug delivery systems in preclinical models. However, the field has great potential, especially with tremendous advances in sophisticated formulation design and understanding of *in vivo* behavior over the years. Each type of drug delivery formulation will encounter different challenges during its clinical translation, yet most formulations will face similar obstacles. In the case of NP-based systems in clinical translation, biological and technical aspects present challenges to drug delivery. Biological challenges include a limited ability to cross biological barriers, the ability for nanomedicines to reach their target cells, increased accumulation, and heterogeneity between animal models and humans. Pegylation is a strategy used to improve the penetration of biological barriers, including limiting interactions and clearance by immune cells and improving delivery [48]. This results in an increased circulation time and the chance for NPs to reach their target site. In addition, polysaccharides such as dextran have been

Table 2. Synthetic retinoid formulations under study in the context of cancer.

Synthetic Retinoid	Formulation	Delivery System	Cancer Models	Key Findings	References/ Country
Fenretinide	4-HPR-PEG2K	Polymeric micelles	Ovarian cancer cells (A2780) Breast cancer cells (MCF-7) BALB/c nude mice xenograft bearing A2780 cells	- Higher <i>in vitro</i> cytotoxicity to A2780 and MCF-7 cells - Reduced plasma elimination clearance of 4-HPR <i>in vivo</i> - Increased systemic circulation time - Enhanced anti-tumor efficacy <i>in vivo</i>	[42]/ China
	Bio-nFeR	Micellar system	Patient-derived CSC lines from primary melanoma, glioblastoma, lung and colon cancers NOD SCID mice xenograft bearing either colon CSC lines or melanoma CSC lines NSG mice xenograft model bearing lung CSC lines	- Increased toxicity against lung CSCs <i>in vitro</i> - Improved plasma exposure - Broad anti-tumor activity <i>in vitro</i> and <i>in vivo</i> - Reduced tumor cell proliferation - Induced apoptosis - Modulation of lipid metabolism - Decreased CSC features	[43]/ Italy
	Fenretinide ME	ME	Breast cancer cells (MCF-7 and T-47) NMU-induced breast cancer model of SD rats	- Reduced cancer cell viability, migration and proliferation - Reduced spheroid viability - The increased ability for the drug to accumulate in the tissue - Increased anti-tumor efficacy <i>in vivo</i>	[58]/ Brazil
	4-HPR/LXS	Lipid matrix	Human patients with relapsed neuroblastoma (Phase I clinical trials)	- Higher plasma levels than the previously used capsule formulation - Minimal toxicity - Anti-tumor activity.	[59]/ United States of America
	Intravenous 4-HPR emulsion	Emulsion	Human patients with malignant solid tumors (Phase I clinical trials)	- Higher plasma steady-state concentrations than previous capsule formations Manageable safety profile	[38]/ United States of America
Bexarotene	DBTP	Nanovesicles	Breast cancer cells (MCF-7) Non--small lung cancer cells (A549)	- Successful internalization and intracellular release of DBTP nanovesicles - Higher <i>in vitro</i> cytotoxicity against breast and lung cancer cells	[92]/ China
	Aerosol bexarotene	Aerosol delivery	Lung cancer cells (H226 and H520) Lung AC model of p53 mutant A/J mice Lung SCC Model of NIH Swiss mice	- Chemopreventive effect against lung cancer <i>in vivo</i> - No visible signs of toxicity - Plasma triglycerides or cholesterol levels were not increased - Increased tumor-infiltrating T cells	[93]/ United States of America
ST1926	ST-NP	NPs	Human AML cells (THP-1, KG1- α , MOLM-13, ML-2 and HEL) Primary AML cells from patients PBMCs from healthy donors NOD SCID mice xenograft-bearing AML cells NSG mice orthotopic bearing THP-1 cells	Enhanced growth inhibitory effects Diminished leukemia bone marrow burden Prolonged survival and reduced peritoneal volume of AML xenografted mice Drug loading content: 7.5 mg/kg ST1926-NP	[107]/ Lebanon
Tamibarotene	Tamibarotene-loaded PLGA microsphere	Microspheres	Kunming mice xenograft bearing HCC H22 cells	Slow and constant release of tamibarotene from formulation for a longer period of time Improved inhibitory effects in HCC models	[120]/ China

Abbreviations: PEG, polyethylene glycol; BALB/c, Bagg albino; Bio-nFeR, Bionanofenretinide; CSC, cancer stem cell; NOD-SCID, non-obese diabetic/severe combined immunodeficiency; NSG, NOD SCID gamma; ME, microemulsion; NMU, N-nitrosu-Nmethylurea; SD, sprague dawley; LXS, LYM-X-SORB™; DBTP, dual bexarotene-tailed phospholipid; AC, adenocarcinoma; SCC, squamous cell carcinoma; NIH, national institute of health; NP, nanoparticle; AML, acute myeloid leukemia; PBMC, peripheral blood mononuclear cells; PLGA, poly (lactic-co-glycolic acid); HCC, hepatocellular carcinoma.

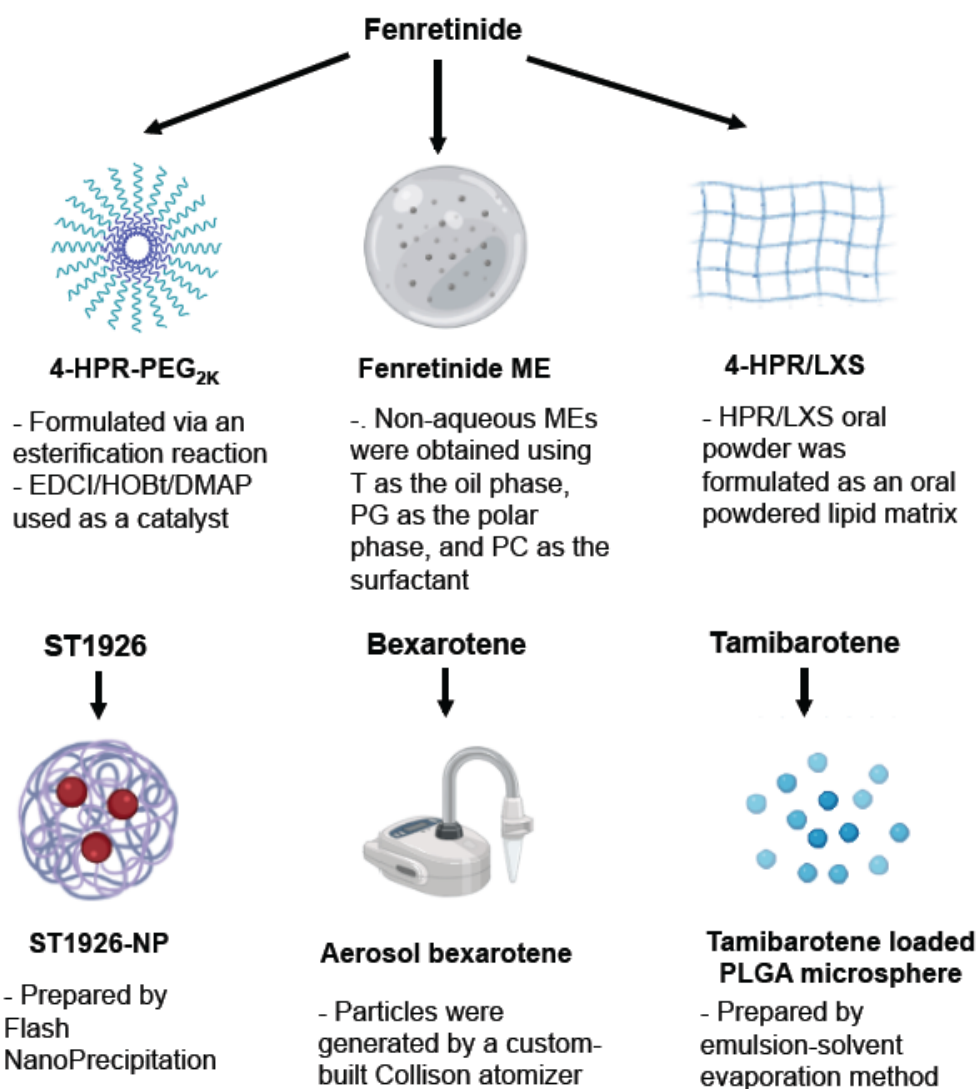


Fig. (2). Synthesis and Preparation of Synthetic Retinoid Formulations. **4-HPR**, fenretinide; **PEG**, polyethylene glycol; **EDCI**, (3-Dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride; **HOBt**, 1-Hydroxybenzotriazole; **DMAP**, 4-dimethylaminopyridine; **ME**, micro-emulsion; **T**, tricaprylin; **PG**, propylene glycol; **PC**, phosphatidylcholine; **LXS**, LYM-X-SORB™; **NP**, nanoparticle; **PLGA**, poly lactic-co-glycolic acid (Adapted by BioRender.com). (A higher resolution / colour version of this figure is available in the electronic copy of the article).

widely used in drug delivery applications due to their biocompatibility and bioavailability [124]. In fact, dextran-coated NPs have been clinically approved to treat anemia [125]. Currently, antibodies conjugated to the surface of NPs against epidermal growth factor receptor and transferrin receptor are being tested in clinical trials [125]. If approved, these drug delivery systems will ease the way for additional antibody-targeted NP systems to reach the clinic.

Among the technical challenges, the scale-up of drug delivery formulations is a major hurdle in pharmaceutical development since most NPs used in preclinical models are synthesized in small batches. Translating a scientific discovery from bench to bedside requires a consistent and highly reproducible formulation process. In many cases, the process of NP formulation requires multiple steps, including homogenization, emulsification, centrifugation, and cross-linking. At the small-scale development of NPs, it would be beneficial to pinpoint and optimize critical parameters and deter-

mine the best approach to use if the product were scaled up. Demonstrating process scale-up is key to moving promising formulations from proof-of-concept toward commercial development.

Despite extensive research in this area, further preclinical and clinical studies need to address the pharmacokinetics and pharmacodynamics nature of synthetic retinoid formulations. This requires the development of synthetic retinoid nano theranostics systems combining imaging, responsiveness, and therapy in a single platform. Some studies worked on developing drug delivery systems containing synthetic retinoids and other drugs. However, further efforts need to be done in this area to control the half-life of each drug in preclinical models as it can pave the way for novel therapeutic approaches. Cancer is a complex and multifactorial disease caused by genetic and epigenetic factors [126]. Therefore, cancer clinical outcomes can be significantly enhanced by administering two or more drugs and fine-tuning their design

in the delivery system. The clinical use of synthetic retinoids can be greatly enhanced by choosing the right parameters, including suitable carriers, polymers, and drug delivery systems. The destabilization phenomena can be avoided by encapsulating retinoids in different drug delivery systems.

CONCLUSION

Synthetic retinoids are an important class of compounds used to treat various medical conditions, including cancer. However, they are limited by their low bioavailability and other related side effects. The development of retinoid formulations provided several advantages for clinical translation, including enhanced bioavailability, photostability, efficacy, and decreased toxicity. In addition to reducing the side effects of retinoids, formulation strategies also improved their pharmacological properties. By altering the different parameters of retinoid formulations, they can be targeted to specific body compartments. Encapsulation of retinoids in different drug delivery systems holds great potential as studies have shown that retinoids are protected and highly stable. Their efficiency was improved in controlled release studies as their bioavailability in the human body was increased.

Studies demonstrated that the anti-tumor activity of retinoids is greatly enhanced with formulations that increase their *in vivo* half-life at tumor sites [127]. The efficacy of synthetic retinoids in cancer treatment has improved through polymeric micelles, NPs, microemulsions, and microspheres, among others. However, the clinical translation of both natural and synthetic retinoids is still lagging. While several hurdles need to be overcome before synthetic retinoid formulations reach the clinic, there is a huge potential for this field in the near future.

LIST OF ABBREVIATIONS

ASD	=	Amorphous Solid Dispersions
EPR	=	Enhanced Permeability and Retention
PEG	=	Poly (Ethylene Glycol)
RA	=	Retinoic Acid
RES	=	Reticuloendothelial System

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This work was supported by the American University of Beirut University Research Board.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors thank Dr. Ali Youssef for his help with Fig. (1) and Dr. Samira Kaissi for her critical review of the manuscript.

REFERENCES

- Gonçalves, A.; Estevinho, B.N.; Rocha, F. Microencapsulation of vitamin A: A review. *Trends Food Sci. Technol.*, **2016**, *51*, 76-87. <http://dx.doi.org/10.1016/j.tifs.2016.03.001>
- Dobrotkova, V.; Chlapek, P.; Mazanek, P.; Sterba, J.; Veselska, R. Traffic lights for retinoids in oncology: Molecular markers of retinoid resistance and sensitivity and their use in the management of cancer differentiation therapy. *BMC Cancer*, **2018**, *18*(1), 1059. <http://dx.doi.org/10.1186/s12885-018-4966-5> PMID: 30384831
- Gudas, L.J. Synthetic retinoids beyond cancer therapy. *Annu. Rev. Pharmacol. Toxicol.*, **2021**, *62*. PMID: 34516292
- Karrer, P.; Morf, R.; Schopp, K. Information on vitamin A from train-oil. *Helv. Chim. Acta*, **1931**, *14*, 1035-1040.
- Khalil, S.; Bardawil, T.; Stephan, C.; Darwiche, N.; Abbas, O.; Kibbi, A.G.; Nemer, G.; Kurban, M. Retinoids: A journey from the molecular structures and mechanisms of action to clinical uses in dermatology and adverse effects. *J. Dermatolog. Treat.*, **2017**, *28*(8), 684-696. <http://dx.doi.org/10.1080/09546634.2017.1309349> PMID: 28318351
- Ablain, J.; de Thé, H. Retinoic acid signaling in cancer: The parable of acute promyelocytic leukemia. *Int. J. Cancer*, **2014**, *135*(10), 2262-2272. <http://dx.doi.org/10.1002/ijc.29081> PMID: 25130873
- Beckenbach, L.; Baron, J.M.; Merk, H.F.; Löffler, H.; Amann, P.M. Retinoid treatment of skin diseases. *Eur. J. Dermatol.*, **2015**, *25*(5), 384-391. <http://dx.doi.org/10.1684/ejd.2015.2544> PMID: 26069148
- Mukherjee, S.; Date, A.; Patravale, V.; Korting, H.C.; Roeder, A.; Weindl, G. Retinoids in the treatment of skin aging: An overview of clinical efficacy and safety. *Clin. Interv. Aging*, **2006**, *1*(4), 327-348. <http://dx.doi.org/10.2147/cia.2006.1.4.327> PMID: 18046911
- Theodosiou, M.; Laudet, V.; Schubert, M. From carrot to clinic: An overview of the retinoic acid signaling pathway. *Cell. Mol. Life Sci.*, **2010**, *67*(9), 1423-1445. <http://dx.doi.org/10.1007/s00018-010-0268-z> PMID: 20140749
- Muindi, J.; Frankel, S.R.; Miller, W.H., Jr; Jakubowski, A.; Scheinberg, D.A.; Young, C.W.; Dmitrovsky, E.; Warrell, R.P., Jr. Continuous treatment with all-trans retinoic acid causes a progressive reduction in plasma drug concentrations: Implications for relapse and retinoid "resistance" in patients with acute promyelocytic leukemia. *Blood*, **1992**, *79*(2), 299-303. <http://dx.doi.org/10.1182/blood.V79.2.299.299> PMID: 1309668
- Szuts, E.Z.; Harosi, F.I. Solubility of retinoids in water. *Arch. Biochem. Biophys.*, **1991**, *287*(2), 297-304. [http://dx.doi.org/10.1016/0003-9861\(91\)90482-X](http://dx.doi.org/10.1016/0003-9861(91)90482-X) PMID: 1898007
- di Masi, A.; Leboffe, L.; De Marinis, E.; Pagano, F.; Cicconi, L.; Rochette-Egly, C.; Lo-Coco, F.; Ascenzi, P.; Nervi, C. Retinoic acid receptors: From molecular mechanisms to cancer therapy. *Mol. Aspects Med.*, **2015**, *41*, 1-115. <http://dx.doi.org/10.1016/j.mam.2014.12.003> PMID: 25543955
- Vahlquist, A. Retinoids and the skin: From vitamin A in human epidermis to the pharmacology of oral retinoids in dermatology. *Basic Clin. Dermatol.*, **2007**, *39*, 55. <http://dx.doi.org/10.3109/9781420021189.003>
- Hail, N., Jr; Kim, H.J.; Lotan, R. Mechanisms of fenretinide-induced apoptosis. *Apoptosis*, **2006**, *11*(10), 1677-1694. <http://dx.doi.org/10.1007/s10495-006-9289-3> PMID: 16850162
- Parella, E.; Gianni, M.; Fratelli, M.; Barzago, M.M.; Raska, I., Jr; Diomedea, L.; Kurosaki, M.; Pisano, C.; Carminati, P.; Merlini, L.; Dallavalle, S.; Tavecchio, M.; Rochette-Egly, C.; Terao, M.; Garattini, E. Antitumor activity of the retinoid-related molecules (E)-3-(4'-hydroxy-3'-adamantylbiphenyl-4-yl)acrylic acid (ST1926) and 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437) in F9 teratocarcinoma: Role of retinoic acid receptor γ and retinoid-independent pathways. *Mol. Pharmacol.*, **2006**, *70*(3), 909-924. <http://dx.doi.org/10.1124/mol.106.023614> PMID: 16788091
- Das, B.C.; Thapa, P.; Karki, R.; Das, S.; Mahapatra, S.; Liu, T-C.; Torregroza, I.; Wallace, D.P.; Kambhampati, S.; Van Veldhuizen, P.; Verma, A.; Ray, S.K.; Evans, T. Retinoic acid signaling pathways in development and diseases. *Bioorg. Med. Chem.*, **2014**, *22*(2), 673-683. <http://dx.doi.org/10.1016/j.bmc.2013.11.025> PMID: 24393720

- [17] Mezquita, B.; Mezquita, C. Two opposing faces of retinoic acid: Induction of stemness or induction of differentiation depending on cell-type. *Biomolecules*, **2019**, *9*(10), 567. <http://dx.doi.org/10.3390/biom9100567> PMID: 31590252
- [18] Tallman, M.S. Acute promyelocytic leukemia as a paradigm for targeted therapy. *Semin. Hematol.*, **2004**, *41*(2 Suppl 4), 27-32.
- [19] Fontana, J.A.; Rishi, A.K. Classical and novel retinoids: Their targets in cancer therapy. *Leukemia*, **2002**, *16*(4), 463-472. <http://dx.doi.org/10.1038/sj.leu.2402414> PMID: 11960323
- [20] Pan, X.Q.; Zheng, X.; Shi, G.; Wang, H.; Ratnam, M.; Lee, R.J. Strategy for the treatment of acute myelogenous leukemia based on folate receptor β -targeted liposomal doxorubicin combined with receptor induction using all-trans retinoic acid. *Blood*, **2002**, *100*(2), 594-602. <http://dx.doi.org/10.1182/blood.V100.2.594> PMID: 12091353
- [21] Ferreira, R.; Napoli, J.; Enver, T.; Bernardino, L.; Ferreira, L. Advances and challenges in retinoid delivery systems in regenerative and therapeutic medicine. *Nat. Commun.*, **2020**, *11*(1), 4265. <http://dx.doi.org/10.1038/s41467-020-18042-2> PMID: 32848154
- [22] Li, Y.; Wongsiriroj, N.; Blaner, W.S. The multifaceted nature of retinoid transport and metabolism. *Hepatobiliary Surg. Nutr.*, **2014**, *3*(3), 126-139. PMID: 25019074
- [23] Kelly, M.; von Lintig, J. STRA6: Role in cellular retinol uptake and efflux. *Hepatobiliary Surg. Nutr.*, **2015**, *4*(4), 229-242. PMID: 26312242
- [24] McKenna, N.J. EMBO Retinoids 2011: Mechanisms, biology and pathology of signaling by retinoic acid and retinoic acid receptors. *Nucl. Recept. Signal.*, **2012**, *10*(1), 10003.
- [25] Brtko, J.; Dvorak, Z. Natural and synthetic retinoid X receptor ligands and their role in selected nuclear receptor action. *Biochimie*, **2020**, *179*, 157-168. <http://dx.doi.org/10.1016/j.biochi.2020.09.027> PMID: 33011201
- [26] Schenk, T.; Stengel, S.; Zelent, A. Unlocking the potential of retinoic acid in anticancer therapy. *Br. J. Cancer*, **2014**, *111*(11), 2039-2045. <http://dx.doi.org/10.1038/bjc.2014.412> PMID: 25412233
- [27] Bastien, J.; Rochette-Egly, C. Nuclear retinoid receptors and the transcription of retinoid-target genes. *Gene*, **2004**, *328*, 1-16. <http://dx.doi.org/10.1016/j.gene.2003.12.005> PMID: 15019979
- [28] Núñez, V.; Alameda, D.; Rico, D.; Mota, R.; Gonzalo, P.; Cedenilla, M.; Fischer, T.; Boscá, L.; Glass, C.K.; Arroyo, A.G.; Ricote, M. Retinoid X receptor α controls innate inflammatory responses through the up-regulation of chemokine expression. *Proc. Natl. Acad. Sci. USA*, **2010**, *107*(23), 10626-10631. <http://dx.doi.org/10.1073/pnas.0913545107> PMID: 20498053
- [29] Chlapek, P.; Slavikova, V.; Mazanek, P.; Sterba, J.; Veselska, R. Why differentiation therapy sometimes fails: Molecular mechanisms of resistance to retinoids. *Int. J. Mol. Sci.*, **2018**, *19*(1), 132. <http://dx.doi.org/10.3390/ijms19010132> PMID: 29301374
- [30] Cosio, T.; Di Prete, M.; Gaziano, R.; Lanna, C.; Orlandi, A.; Di Francesco, P.; Bianchi, L.; Campione, E. Trifarotene: A current review and perspectives in dermatology. *Biomedicines*, **2021**, *9*(3), 237. <http://dx.doi.org/10.3390/biomedicines9030237> PMID: 33652835
- [31] Nguyen, T.H.; Koneru, B.; Wei, S.-J.; Chen, W.H.; Makena, M.R.; Urias, E.; Kang, M.H.; Reynolds, C.P. Fenretinide *via* NOXA Induction, enhanced activity of the BCL-2 inhibitor venetoclax in high BCL-2-expressing neuroblastoma preclinical models. *Mol. Cancer Ther.*, **2019**, *18*(12), 2270-2282. <http://dx.doi.org/10.1158/1535-7163.MCT-19-0385> PMID: 31484706
- [32] Liu, L.; Liu, J.; Wang, H.; Zhao, H.; Du, Y. Fenretinide targeting of human colon cancer sphere cells through cell cycle regulation and stress-responsive activities. *Oncol. Lett.*, **2018**, *16*(4), 5339-5348. <http://dx.doi.org/10.3892/ol.2018.9296> PMID: 30250604
- [33] Zhang, L.; Huang, D.; Shao, D.; Liu, H.; Zhou, Q.; Gui, S.; Wei, W.; Wang, Y. Fenretinide inhibits the proliferation and migration of human liver cancer HepG2 cells by downregulating the activation of myosin light chain kinase through the p38-MAPK signaling pathway. *Oncol. Rep.*, **2018**, *40*(1), 518-526. <http://dx.doi.org/10.3892/or.2018.6436> PMID: 29767236
- [34] Wang, H.; Zhang, Y.; Du, Y. Ovarian and breast cancer spheres are similar in transcriptomic features and sensitive to fenretinide. *Bio-mol. Res. Int.*, **2013**, *2013*, 510905. <http://dx.doi.org/10.1155/2013/510905>
- [35] Song, M.M.; Makena, M.R.; Hindle, A.; Koneru, B.; Nguyen, T.H.; Verlekar, D.U.; Cho, H.; Maurer, B.J.; Kang, M.H.; Reynolds, C.P. Cytotoxicity and molecular activity of fenretinide and metabolites in T-cell lymphoid malignancy, neuroblastoma, and ovarian cancer cell lines in physiological hypoxia. *Anticancer Drugs*, **2019**, *30*(2), 117-127. <http://dx.doi.org/10.1097/CAD.0000000000000696> PMID: 30272587
- [36] Mittal, N.; Malpani, S.; Dyson, M.; Ono, M.; Coon, J.S.; Kim, J.J.; Schink, J.C.; Bulun, S.E.; Pavone, M.E. Fenretinide: A novel treatment for endometrial cancer. *PLoS One*, **2014**, *9*(10), e110410. <http://dx.doi.org/10.1371/journal.pone.0110410> PMID: 25340777
- [37] Xiong, J.; Kuang, X.; Lu, T.; Liu, X.; Cheng, B.; Wang, W.; Wei, D.; Li, X.; Zhang, Z.; Fang, Q.; Wu, D.; Wang, J. Fenretinide-induced apoptosis of acute myeloid leukemia cells *via* NR4A1 translocation into mitochondria and Bcl-2 transformation. *J. Cancer*, **2019**, *10*(27), 6767-6778. <http://dx.doi.org/10.7150/jca.32167> PMID: 31839811
- [38] Thomas, J.S.; El-Khoueiry, A.B.; Maurer, B.J.; Groshen, S.; Pinski, J.K.; Cobos, E.; Gandara, D.R.; Lenz, H.J.; Kang, M.H.; Reynolds, C.P.; Newman, E.M. A phase I study of intravenous fenretinide (4-HPR) for patients with malignant solid tumors. *Cancer Chemother. Pharmacol.*, **2021**, *87*(4), 525-532. <http://dx.doi.org/10.1007/s00280-020-04224-8> PMID: 33423090
- [39] Mohrbacher, A.M.; Yang, A.S.; Groshen, S.; Kummar, S.; Gutierrez, M.E.; Kang, M.H.; Tsao-Wei, D.; Reynolds, C.P.; Newman, E.M.; Maurer, B.J. Phase I study of fenretinide delivered intravenously in patients with relapsed or refractory hematologic malignancies: A California Cancer Consortium Trial. *Clin. Cancer Res.*, **2017**, *23*(16), 4550-4555. <http://dx.doi.org/10.1158/1078-0432.CCR-17-0234> PMID: 28420721
- [40] Cooper, J.P.; Reynolds, C.P.; Cho, H.; Kang, M.H. Clinical development of fenretinide as an antineoplastic drug: Pharmacology perspectives. *Exp. Biol. Med. (Maywood)*, **2017**, *242*(11), 1178-1184. <http://dx.doi.org/10.1177/1535370217706952> PMID: 28429653
- [41] Villablanca, J.G.; London, W.B.; Naranjo, A.; McGrady, P.; Ames, M.M.; Reid, J.M.; McGovern, R.M.; Buhrow, S.A.; Jackson, H.; Stranzinger, E.; Kitchen, B.J.; Sondel, P.M.; Parisi, M.T.; Shulkin, B.; Yanik, G.A.; Cohn, S.L.; Reynolds, C.P. Phase II study of oral capsular 4-hydroxyphenylretinamide (4-HPR/fenretinide) in pediatric patients with refractory or recurrent neuroblastoma: A report from the Children's Oncology Group. *Clin. Cancer Res.*, **2011**, *17*(21), 6858-6866. <http://dx.doi.org/10.1158/1078-0432.CCR-11-0995> PMID: 21908574
- [42] Wang, Y.; Ding, Y.; Wang, C.; Gao, M.; Xu, Y.; Ma, X.; Ma, X.; Cui, H.; Li, L. Fenretinide-polyethylene glycol (PEG) conjugate with improved solubility enhanced cytotoxicity to cancer cell and potent *in vivo* efficacy. *Pharm. Dev. Technol.*, **2020**, *25*(8), 962-970. <http://dx.doi.org/10.1080/10837450.2020.1765377> PMID: 32366203
- [43] Orienti, I.; Salvati, V.; Sette, G.; Zucchetti, M.; Bongiorno-Borbone, L.; Peschiaroli, A.; Zolla, L.; Francescangeli, F.; Ferrari, M.; Matteo, C.; Bello, E.; Di Virgilio, A.; Falchi, M.; De Angelis, M.L.; Baiocchi, M.; Melino, G.; De Maria, R.; Zeuner, A.; Eramo, A. A novel oral micellar fenretinide formulation with enhanced bioavailability and antitumor activity against multiple tumours from cancer stem cells. *J. Exp. Clin. Cancer Res.*, **2019**, *38*(1), 373. <http://dx.doi.org/10.1186/s13046-019-1383-9> PMID: 31439019
- [44] Torchilin, V.P. Targeted polymeric micelles for delivery of poorly soluble drugs. *Cell. Mol. Life Sci.*, **2004**, *61*(19-20), 2549-2559. <http://dx.doi.org/10.1007/s00018-004-4153-5> PMID: 15526161
- [45] Kwon, G. S. Polymeric micelles for delivery of poorly water-soluble compounds. *Crit. Rev. Ther. Drug Carrier Syst.*, **2003**, *20*(5), 357-403.
- [46] Okuda, T.; Kawakami, S.; Higuchi, Y.; Satoh, T.; Oka, Y.; Yokoyama, M.; Yamashita, F.; Hashida, M. Enhanced *in vivo* antitumor

- efficacy of fenretinide encapsulated in polymeric micelles. *Int. J. Pharm.*, **2009**, 373(1-2), 100-106.
<http://dx.doi.org/10.1016/j.ijpharm.2009.01.019> PMID: 19429294
- [47] Maeda, H. The enhanced permeability and retention (EPR) effect in tumor vasculature: The key role of tumor-selective macromolecular drug targeting. *Adv. Enzyme Regul.*, **2001**, 41, 189-207.
[http://dx.doi.org/10.1016/S0065-2571\(00\)00013-3](http://dx.doi.org/10.1016/S0065-2571(00)00013-3) PMID: 11384745
- [48] Suk, J.S.; Xu, Q.; Kim, N.; Hanes, J.; Ensign, L.M. PEGylation as a strategy for improving nanoparticle-based drug and gene delivery. *Adv. Drug Deliv. Rev.*, **2016**, 99(Pt A), 28-51.
<http://dx.doi.org/10.1016/j.addr.2015.09.012> PMID: 26456916
- [49] Gao, H.; Liu, J.; Yang, C.; Cheng, T.; Chu, L.; Xu, H.; Meng, A.; Fan, S.; Shi, L.; Liu, J. The impact of PEGylation patterns on the *in vivo* biodistribution of mixed shell micelles. *Int. J. Nanomedicine*, **2013**, 8, 4229-4246.
 PMID: 24235825
- [50] Fang, J.; Nakamura, H.; Maeda, H. The EPR effect: Unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect. *Adv. Drug Deliv. Rev.*, **2011**, 63(3), 136-151.
<http://dx.doi.org/10.1016/j.addr.2010.04.009> PMID: 20441782
- [51] Formelli, F.; Cavadini, E.; Luksch, R.; Garaventa, A.; Villani, M.G.; Appierto, V.; Persiani, S. Pharmacokinetics of oral fenretinide in neuroblastoma patients: Indications for optimal dose and dosing schedule also with respect to the active metabolite 4-oxo-fenretinide. *Cancer Chemother. Pharmacol.*, **2008**, 62(4), 655-665.
<http://dx.doi.org/10.1007/s00280-007-0649-7> PMID: 18066548
- [52] Ma, X.; Williams, R.O., III Characterization of amorphous solid dispersions: An update. *J. Drug Deliv. Sci. Technol.*, **2019**, 50, 113-124.
<http://dx.doi.org/10.1016/j.jddst.2019.01.017>
- [53] Margarit, M.V.; Marin, M.T.; Contreras, M.D. Solubility of solid dispersions of pizotifen malate and povidone. *Drug Dev. Ind. Pharm.*, **2001**, 27(6), 517-522.
<http://dx.doi.org/10.1081/DDC-100105176> PMID: 11548858
- [54] Bhardwaj, S.P.; Arora, K.K.; Kwong, E.; Templeton, A.; Clas, S.D.; Suryanarayanan, R. Mechanism of amorphous itraconazole stabilization in polymer solid dispersions: Role of molecular mobility. *Mol. Pharm.*, **2014**, 11(11), 4228-4237.
<http://dx.doi.org/10.1021/mp5004515> PMID: 25325389
- [55] Laurent, P.; Betancourt, A.; Lemieux, M.; Thibert, R. Solid oral formulations of fenretinide. W.O. Patent 2016011535A1, **2016**.
- [56] Zhang, Y.; Wischke, C.; Mittal, S.; Mitra, A.; Schwendeman, S.P. Design of controlled release PLGA microspheres for hydrophobic fenretinide. *Mol. Pharm.*, **2016**, 13(8), 2622-2630.
<http://dx.doi.org/10.1021/acs.molpharmaceut.5b00961> PMID: 27144450
- [57] Nieto, K.; Mallery, S.R.; Schwendeman, S.P. Microencapsulation of amorphous solid dispersions of fenretinide enhances drug solubility and release from PLGA *in vitro* and *in vivo*. *Int. J. Pharm.*, **2020**, 586, 119475.
<http://dx.doi.org/10.1016/j.ijpharm.2020.119475> PMID: 32525080
- [58] Salata, G.C.; Malagó, I.D.; Carvalho Dartora, V.F.M.; Marçal Pessoa, A.F.; Fantini, M.C.A.; Costa, S.K.P.; Machado-Neto, J.A.; Lopes, L.B. Microemulsion for prolonged release of fenretinide in the mammary tissue and prevention of breast cancer development. *Mol. Pharm.*, **2021**, 18(9), 3401-3417.
<http://dx.doi.org/10.1021/acs.molpharmaceut.1c00319> PMID: 34482696
- [59] Maurer, B.J.; Kang, M.H.; Villablanca, J.G.; Janeba, J.; Groshen, S.; Matthay, K.K.; Sondel, P.M.; Maris, J.M.; Jackson, H.A.; Goodarzian, F.; Shimada, H.; Czarnecki, S.; Hasenauer, B.; Reynolds, C.P.; Marachelian, A. Phase I trial of fenretinide delivered orally in a novel organized lipid complex in patients with re-lapsed/refractory neuroblastoma: A report from the New Approaches to Neuroblastoma Therapy (NANT) consortium. *Pediatr. Blood Cancer*, **2013**, 60(11), 1801-1808.
<http://dx.doi.org/10.1002/pbc.24643> PMID: 23813912
- [60] Maurer, B.J.; Glade Bender, J.L.; Kang, M.H.; Villablanca, J.; Wei, D.; Groshen, S.G.; Yang, S.; Czarnecki, S.; Granger, M.P.; Katzenstein, H.M. Fenretinide (4-HPR)/Lym-X-Sorb (LXS) oral powder plus ketoconazole in patients with high-risk (HR) recurrent or resistant neuroblastoma: A New Approach to Neuroblastoma Therapy (NANT) Consortium trial. *J. Clin. Oncol.*, **2014**, 32(Suppl 15), 10071.
- [61] Liu, X.; Maurer, B.; Frgala, T.; Page, J.; Noker, P.; Fulton, R.; Ames, M.; Reid, J.; Gupta, S.; Vishnuvajjala, R. Preclinical toxicology and pharmacokinetics of intravenous lipid emulsion fenretinide. *Mol. Cancer Ther.*, **2007**, 6(Suppl 11), C159.
- [62] Bayat Mokhtari, R.; Homayouni, T.S.; Baluch, N.; Morgatskaya, E.; Kumar, S.; Das, B.; Yeager, H. Combination therapy in combating cancer. *Oncotarget*, **2017**, 8(23), 38022-38043.
<http://dx.doi.org/10.18632/oncotarget.16723> PMID: 28410237
- [63] Vivat-Hannah, V.; You, D.; Rizzo, C.; Daris, J-P.; Lapointe, P.; Zusi, F.C.; Marinier, A.; Lorenzi, M.V.; Gottardis, M.M. Synergistic cytotoxicity exhibited by combination treatment of selective retinoid ligands with taxol (Paclitaxel). *Cancer Res.*, **2001**, 61(24), 8703-8711.
 PMID: 11751388
- [64] Jordan, M.A. Mechanism of action of antitumor drugs that interact with microtubules and tubulin. *Curr. Med. Chem. Anticancer Agents*, **2002**, 2(1), 1-17.
<http://dx.doi.org/10.2174/1568011023354290> PMID: 12678749
- [65] Sun, Y.; Yu, B.; Wang, G.; Wu, Y.; Zhang, X.; Chen, Y.; Tang, S.; Yuan, Y.; Lee, R.J.; Teng, L.; Xu, S. Enhanced antitumor efficacy of vitamin E TPGS-emulsified PLGA nanoparticles for delivery of paclitaxel. *Colloids Surf. B Biointerfaces*, **2014**, 123, 716-723.
<http://dx.doi.org/10.1016/j.colsurfb.2014.10.007> PMID: 25456995
- [66] Janardhanan, R.; Butler, J.T.; Banik, N.L.; Ray, S.K. N-(4-Hydroxyphenyl) retinamide potentiated paclitaxel for cell cycle arrest and apoptosis in glioblastoma C6 and RG2 cells. *Brain Res.*, **2009**, 1268, 142-153.
<http://dx.doi.org/10.1016/j.brainres.2009.02.064> PMID: 19285047
- [67] Hu, M.; Zhang, J.; Ding, R.; Fu, Y.; Gong, T.; Zhang, Z. Improved oral bioavailability and therapeutic efficacy of dabigatran etexilate via Soluplus-TPGS binary mixed micelles system. *Drug Dev. Ind. Pharm.*, **2017**, 43(4), 687-697.
<http://dx.doi.org/10.1080/03639045.2016.1278015> PMID: 28032534
- [68] Jin, X.; Zhou, B.; Xue, L.; San, W. Soluplus® micelles as a potential drug delivery system for reversal of resistant tumor. *Biomed. Pharmacother.*, **2015**, 69, 388-395.
<http://dx.doi.org/10.1016/j.biopha.2014.12.028> PMID: 25661387
- [69] Wang, Y.; Ding, Y.; Xu, Y.; Wang, C.; Ding, Y.; Gao, M.; Ma, C.; Ma, X.; Li, L. Mixed micelles of TPGS and Soluplus® for co-delivery of paclitaxel and fenretinide: *In vitro* and *in vivo* anticancer study. *Pharm. Dev. Technol.*, **2020**, 25(7), 865-873.
<http://dx.doi.org/10.1080/10837450.2020.1753770> PMID: 32266855
- [70] Orienti, I.; Francescangeli, F.; De Angelis, M.L.; Fecchi, K.; Bongiorno-Borbone, L.; Signore, M.; Peschiaroli, A.; Boe, A.; Bruselles, A.; Costantino, A.; Eramo, A.; Salvati, V.; Sette, G.; Contavalli, P.; Zolla, L.; Oki, T.; Kitamura, T.; Spada, M.; Giuliani, A.; Baiocchi, M.; La Torre, F.; Melino, G.; Tartaglia, M.; De Maria, R.; Zeuner, A. A new bioavailable fenretinide formulation with anti-proliferative, antimetabolic, and cytotoxic effects on solid tumors. *Cell Death Dis.*, **2019**, 10(7), 529.
<http://dx.doi.org/10.1038/s41419-019-1775-y> PMID: 31332161
- [71] Kotla, V.; Goel, S.; Nischal, S.; Heuck, C.; Vivek, K.; Das, B.; Verma, A. Mechanism of action of lenalidomide in hematological malignancies. *J. Hematol. Oncol.*, **2009**, 2(1), 36.
<http://dx.doi.org/10.1186/1756-8722-2-36> PMID: 19674465
- [72] Lu, L.; Payvandi, F.; Wu, L.; Zhang, L-H.; Hariri, R.J.; Man, H-W.; Chen, R.S.; Muller, G.W.; Hughes, C.C.; Stirling, D.I.; Schaffer, P.H.; Bartlett, J.B. The anti-cancer drug lenalidomide inhibits angiogenesis and metastasis via multiple inhibitory effects on endothelial cell function in normoxic and hypoxic conditions. *Microvasc. Res.*, **2009**, 77(2), 78-86.
<http://dx.doi.org/10.1016/j.mvr.2008.08.003> PMID: 18805433
- [73] Moodad, S.; El Hajj, R.; Hleihel, R.; Hajjar, L.; Tawil, N.; Karam, M.; Hamie, M.; Abou Merhi, R.; El Sabban, M.; El Hajj, H. Lenalidomide in combination with arsenic trioxide: An effective therapy for primary effusion lymphoma. *Cancers (Basel)*, **2020**, 12(9), 2483.
<http://dx.doi.org/10.3390/cancers12092483> PMID: 32883022
- [74] Xu, Y.; Sun, J.; Sheard, M.A.; Tran, H.C.; Wan, Z.; Liu, W.Y.; Asgharzadeh, S.; Sposto, R.; Wu, H.W.; Seeger, R.C. Lenalido-

- mid overcomes suppression of human natural killer cell anti-tumor functions by neuroblastoma microenvironment-associated IL-6 and TGFβ1. *Cancer Immunol. Immunother.*, **2013**, 62(10), 1637-1648. <http://dx.doi.org/10.1007/s00262-013-1466-y> PMID: 23982484
- [75] Orienti, I.; Nguyen, F.; Guan, P.; Kolla, V.; Calonghi, N.; Farruggia, G.; Chorny, M.; Brodeur, G.M. A novel nanomicellar combination of fenretinide and lenalidomide shows marked antitumor activity in a neuroblastoma xenograft model. *Drug Des. Devel. Ther.*, **2019**, 13, 4305-4319. <http://dx.doi.org/10.2147/DDDT.S221909> PMID: 31908416
- [76] Hermann, T.W.; Yen, W.-C.; Tooker, P.; Fan, B.; Roegner, K.; Negro-Vilar, A.; Lamph, W.W.; Bissonnette, R.P. The retinoid X receptor agonist bexarotene (Targretin) synergistically enhances the growth inhibitory activity of cytotoxic drugs in non-small cell lung cancer cells. *Lung Cancer*, **2005**, 50(1), 9-18. <http://dx.doi.org/10.1016/j.lungcan.2005.05.008> PMID: 15993980
- [77] Germain, P.; Chambon, P.; Eichele, G.; Evans, R.M.; Lazar, M.A.; Leid, M.; De Lera, A.R.; Lotan, R.; Mangelsdorf, D.J.; Gronemeyer, H. International union of pharmacology. LXIII. Retinoid X receptors. *Pharmacol. Rev.*, **2006**, 58(4), 760-772. <http://dx.doi.org/10.1124/pr.58.4.7> PMID: 17132853
- [78] Qi, L.; Guo, Y.; Zhang, P.; Cao, X.; Luan, Y. Preventive and therapeutic effects of the retinoid X receptor agonist bexarotene on tumors. *Curr. Drug Metab.*, **2016**, 17(2), 118-128. <http://dx.doi.org/10.2174/138920021702160114121706> PMID: 26806040
- [79] Duvic, M.; Hymes, K.; Heald, P.; Breneman, D.; Martin, A.G.; Myskowski, P.; Crowley, C.; Yocum, R.C. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: Multinational phase II-III trial results. *J. Clin. Oncol.*, **2001**, 19(9), 2456-2471. <http://dx.doi.org/10.1200/JCO.2001.19.9.2456> PMID: 11331325
- [80] Kizaki, M.; Dawson, M. I.; Heyman, R.; Elster, E.; Morosetti, R.; Pakkala, S.; Chen, D.-L.; Ueno, H.; Chao, W.-R.; Morikawa, M. Effects of novel retinoid X receptor-selective ligands on myeloid leukemia differentiation and proliferation *in vitro*. *Blood*, **1996**, 87(5), 1977-84.
- [81] Li, Y.; Zhang, Y.; Hill, J.; Kim, H.-T.; Shen, Q.; Bissonnette, R.P.; Lamph, W.W.; Brown, P.H. The retinoid, bexarotene, prevents the development of premalignant lesions in MMTV-erbB2 mice. *Br. J. Cancer*, **2008**, 98(8), 1380-1388. <http://dx.doi.org/10.1038/sj.bjc.6604320> PMID: 18362934
- [82] Graeppi-Dulac, J.; Vlaeminck-Guillem, V.; Perier-Muzet, M.; Dalle, S.; Orgiazzi, J. Endocrine side-effects of anti-cancer drugs: The impact of retinoids on the thyroid axis. *Eur. J. Endocrinol.*, **2014**, 170(6), R253-R262. <http://dx.doi.org/10.1530/EJE-13-0920> PMID: 24616413
- [83] Qi, L.; Guo, Y.; Luan, J.; Zhang, D.; Zhao, Z.; Luan, Y. Folate-modified bexarotene-loaded bovine serum albumin nanoparticles as a promising tumor-targeting delivery system. *J. Mater. Chem. B Mater. Biol. Med.*, **2014**, 2(47), 8361-8371. <http://dx.doi.org/10.1039/C4TB01102C> PMID: 32262006
- [84] Vasile, A.; Ignat, M.; Zaltariov, M.F.; Sacarescu, L.; Stoleriu, I.; Draganescu, D.; Dumitras, M.; Ochiuz, L. Development of new bexarotene-loaded mesoporous silica systems for topical pharmaceutical formulations. *Acta Chim. Slov.*, **2018**, 65(1), 97-107. <http://dx.doi.org/10.17344/acsi.2017.3641> PMID: 29562115
- [85] Junghanns, J.-U.A.; Müller, R.H. Nanocrystal technology, drug delivery and clinical applications. *Int. J. Nanomedicine*, **2008**, 3(3), 295-309. PMID: 18990939
- [86] Li, L.; Liu, Y.; Wang, J.; Chen, L.; Zhang, W.; Yan, X. Preparation, *in vitro* and *in vivo* evaluation of bexarotene nanocrystals with surface modification by folate-chitosan conjugates. *Drug Deliv.*, **2016**, 23(1), 79-87. <http://dx.doi.org/10.3109/10717544.2014.904455> PMID: 24786485
- [87] Pardeike, J.; Strohmeier, D.M.; Schrödl, N.; Voura, C.; Gruber, M.; Khinast, J.G.; Zimmer, A. Nanosuspensions as advanced printing ink for accurate dosing of poorly soluble drugs in personalized medicines. *Int. J. Pharm.*, **2011**, 420(1), 93-100. <http://dx.doi.org/10.1016/j.ijpharm.2011.08.033> PMID: 21889582
- [88] Jarvis, M.; Krishnan, V.; Mitragotri, S. Nanocrystals: A perspective on translational research and clinical studies. *Bioeng. Transl. Med.*, **2018**, 4(1), 5-16. <http://dx.doi.org/10.1002/btm2.10122> PMID: 30680314
- [89] Chen, L.; Wang, Y.; Zhang, J.; Hao, L.; Guo, H.; Lou, H.; Zhang, D. Bexarotene nanocrystal-Oral and parenteral formulation development, characterization and pharmacokinetic evaluation. *Eur. J. Pharm. Biopharm.*, **2014**, 87(1), 160-169. <http://dx.doi.org/10.1016/j.ejpb.2013.12.005> PMID: 24333772
- [90] Wang, Y.; Rong, J.; Zhang, J.; Liu, Y.; Meng, X.; Guo, H.; Liu, H.; Chen, L. Morphology, *in vivo* distribution and antitumor activity of bexarotene nanocrystals in lung cancer. *Drug Dev. Ind. Pharm.*, **2017**, 43(1), 132-141. <http://dx.doi.org/10.1080/03639045.2016.1225752> PMID: 27588517
- [91] Zhao, Y.; Chen, F.; Pan, Y.; Li, Z.; Xue, X.; Okeke, C.I.; Wang, Y.; Li, C.; Peng, L.; Wang, P.C.; Ma, X.; Liang, X.J. Nanodrug formed by coassembly of dual anticancer drugs to inhibit cancer cell drug resistance. *ACS Appl. Mater. Interfaces*, **2015**, 7(34), 19295-19305. <http://dx.doi.org/10.1021/acsami.5b05347> PMID: 26270258
- [92] He, R.; Du, Y.; Ling, L.; Ismail, M.; Hou, Y.; Yao, C.; Li, X. Nanof ormulation of dual bexarotene-tailed phospholipid conjugate with high drug loading. *Eur. J. Pharm. Sci.*, **2017**, 100, 197-204. <http://dx.doi.org/10.1016/j.ejps.2017.01.012> PMID: 28088372
- [93] Zhang, Q.; Lee, S.B.; Chen, X.; Stevenson, M.E.; Pan, J.; Xiong, D.; Zhou, Y.; Miller, M.S.; Lubet, R.A.; Wang, Y.; Mirza, S.P.; You, M. Optimized bexarotene aerosol formulation inhibits major subtypes of lung cancer in mice. *Nano Lett.*, **2019**, 19(4), 2231-2242. <http://dx.doi.org/10.1021/acs.nanolett.8b04309> PMID: 30873838
- [94] Cincinelli, R.; Dallavalle, S.; Merlini, L.; Penco, S.; Pisano, C.; Carminati, P.; Giannini, G.; Vesce, L.; Gaetano, C.; Illy, B.; Zucco, V.; Supino, R.; Zunino, F. A novel atypical retinoid endowed with proapoptotic and antitumor activity. *J. Med. Chem.*, **2003**, 46(6), 909-912. <http://dx.doi.org/10.1021/jm025593y> PMID: 12620066
- [95] Garattini, E.; Parrella, E.; Diomedede, L.; Gianni, M.; Kalac, Y.; Merlini, L.; Simoni, D.; Zanier, R.; Ferrara, F.F.; Chiarucci, I.; Carminati, P.; Terao, M.; Pisano, C. ST1926, a novel and orally active retinoid-related molecule inducing apoptosis in myeloid leukemia cells: Modulation of intracellular calcium homeostasis. *Blood*, **2004**, 103(1), 194-207. <http://dx.doi.org/10.1182/blood-2003-05-1577> PMID: 12958071
- [96] Di Francesco, A.M.; Meco, D.; Torella, A.R.; Barone, G.; D'Incalci, M.; Pisano, C.; Carminati, P.; Riccardi, R. The novel atypical retinoid ST1926 is active in ATRA resistant neuroblastoma cells acting by a different mechanism. *Biochem. Pharmacol.*, **2007**, 73(5), 643-655. <http://dx.doi.org/10.1016/j.bcp.2006.10.033> PMID: 17150196
- [97] Basma, H.; Ghayad, S.E.; Rammal, G.; Mancinelli, A.; Harajly, M.; Ghamloush, F.; Dweik, L.; El-Eit, R.; Zalzali, H.; Rabeh, W.; Pisano, C.; Darwiche, N.; Saab, R. The synthetic retinoid ST1926 as a novel therapeutic agent in rhabdomyosarcoma. *Int. J. Cancer*, **2016**, 138(6), 1528-1537. <http://dx.doi.org/10.1002/ijc.29886> PMID: 26453552
- [98] Zucco, V.; Benedetti, V.; De Cesare, M.; Zunino, F. Sensitization of ovarian carcinoma cells to the atypical retinoid ST1926 by the histone deacetylase inhibitor, RC307: Enhanced DNA damage response. *Int. J. Cancer*, **2010**, 126(5), 1246-1255. PMID: 19676051
- [99] El Hajj, H.; Khalil, B.; Ghandour, B.; Nasr, R.; Shahine, S.; Ghan-tous, A.; Abdel-Samad, R.; Sinjab, A.; Hasegawa, H.; Jabbour, M.; Hall, W.W.; Zaatari, G.; Dbaibo, G.; Pisano, C.; Bazarbachi, A.; Darwiche, N. Preclinical efficacy of the synthetic retinoid ST1926 for treating adult T-cell leukemia/lymphoma. *Blood*, **2014**, 124(13), 2072-2080. <http://dx.doi.org/10.1182/blood-2014-03-560060> PMID: 25035162
- [100] Nasr, R.R.; Hmadi, R.A.; El-Eit, R.M.; Iskandarani, A.N.; Jabbour, M.N.; Zaatari, G.S.; Mahon, F.X.; Pisano, C.C.; Darwiche, N.D. ST1926, an orally active synthetic retinoid, induces apoptosis in chronic myeloid leukemia cells and prolongs survival in a murine model. *Int. J. Cancer*, **2015**, 137(3), 698-709. <http://dx.doi.org/10.1002/ijc.29407> PMID: 25557649
- [101] Karam, L.; Houshaymi, B.; Abdel-Samad, R.; Jaafar, M.; Halloum, I.; Pisano, C.; Neipel, F.; Darwiche, N.; Abou Merhi, R. Antitumor activity of the synthetic retinoid ST1926 on primary effusion lym-

- phoma *in vitro* and *in vivo* models. *Oncol. Rep.*, **2018**, *39*(2), 721-730.
PMID: 29207182
- [102] Aouad, P.; Saikali, M.; Abdel-Samad, R.; Fostok, S.; El-Houjeiri, L.; Pisano, C.; Talhouk, R.; Darwiche, N. Antitumor activities of the synthetic retinoid ST1926 in two-dimensional and three-dimensional human breast cancer models. *Anticancer Drugs*, **2017**, *28*(7), 757-770.
<http://dx.doi.org/10.1097/CAD.0000000000000511> PMID: 28471809
- [103] Bahmad, H.F.; Samman, H.; Monzer, A.; Hadadeh, O.; Cheaito, K.; Abdel-Samad, R.; Hayar, B.; Pisano, C.; Msheik, H.; Liu, Y.N.; Darwiche, N.; Abou-Kheir, W. The synthetic retinoid ST1926 attenuates prostate cancer growth and potentially targets prostate cancer stem-like cells. *Mol. Carcinog.*, **2019**, *58*(7), 1208-1220.
<http://dx.doi.org/10.1002/mc.23004> PMID: 30883933
- [104] Abdel-Samad, R.; Aouad, P.; Gali-Muhtasib, H.; Sweidan, Z.; Hmadi, R.; Kadara, H.; D'Andrea, E.L.; Fucci, A.; Pisano, C.; Darwiche, N. Mechanism of action of the atypical retinoid ST1926 in colorectal cancer: DNA damage and DNA polymerase α . *Am. J. Cancer Res.*, **2018**, *8*(1), 39-55.
PMID: 29416919
- [105] Valli, C.; Paroni, G.; Di Francesco, A.M.; Riccardi, R.; Tavecchio, M.; Erba, E.; Boldetti, A.; Gianni, M.; Fratelli, M.; Pisano, C.; Merlini, L.; Antocchia, A.; Cenciarelli, C.; Terao, M.; Garattini, E. Atypical retinoids ST1926 and CD437 are S-phase-specific agents causing DNA double-strand breaks: Significance for the cytotoxic and antiproliferative activity. *Mol. Cancer Ther.*, **2008**, *7*(9), 2941-2954.
<http://dx.doi.org/10.1158/1535-7163.MCT-08-0419> PMID: 18790775
- [106] Sala, F.; Zucchetti, M.; Bagnati, R.; D'Incalci, M.; Pace, S.; Capocasa, F.; Marangon, E. Development and validation of a liquid chromatography-tandem mass spectrometry method for the determination of ST1926, a novel oral antitumor agent, adamantyl retinoid derivative, in plasma of patients in a Phase I study. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.*, **2009**, *877*(27), 3118-3126.
<http://dx.doi.org/10.1016/j.jchromb.2009.08.001> PMID: 19695967
- [107] El-Houjeiri, L.; Saad, W.; Hayar, B.; Aouad, P.; Tawil, N.; Abdel-Samad, R.; Hleihel, R.; Hamie, M.; Mancinelli, A.; Pisano, C.; El Hajj, H.; Darwiche, N. Antitumor effect of the atypical retinoid ST1926 in acute myeloid leukemia and nanoparticle formulation prolongs lifespan and reduces tumor burden of xenograft mice. *Mol. Cancer Ther.*, **2017**, *16*(10), 2047-2057.
<http://dx.doi.org/10.1158/1535-7163.MCT-16-0785> PMID: 28619754
- [108] Tong, R.; Kohane, D.S. New strategies in cancer nanomedicine. *Annu. Rev. Pharmacol. Toxicol.*, **2016**, *56*, 41-57.
<http://dx.doi.org/10.1146/annurev-pharmtox-010715-103456> PMID: 26514197
- [109] Wicki, A.; Witzigmann, D.; Balasubramanian, V.; Huwyler, J. Nanomedicine in cancer therapy: Challenges, opportunities, and clinical applications. *J. Control. Release*, **2015**, *200*, 138-157.
<http://dx.doi.org/10.1016/j.jconrel.2014.12.030> PMID: 25545217
- [110] Barenholz, Y. Doxil[®]--the first FDA-approved nano-drug: Lessons learned. *J. Control. Release*, **2012**, *160*(2), 117-134.
<http://dx.doi.org/10.1016/j.jconrel.2012.03.020> PMID: 22484195
- [111] Green, M.R.; Manikhas, G.M.; Orlov, S.; Afanasyev, B.; Makhson, A.M.; Bhar, P.; Hawkins, M.J. Abraxane, a novel Cremophor-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. *Ann. Oncol.*, **2006**, *17*(8), 1263-1268.
<http://dx.doi.org/10.1093/annonc/mdl104> PMID: 16740598
- [112] Fda.gov. FDA approves Abraxane for late-stage pancreatic cancer injectable. Available from: <http://www.fda.gov/NewsEvents/> (Accessed on: 1 May 2016).
- [113] Simon, A.M.; Jagadeeshan, S.; Abraham, E.; Akhilandeshwaran, A.; Pillai, J.J.; Kumar, N.A.; Sivakumari, A.N.; Kumar, G.S. Poly (D,L-lactic-co-glycolide) nanoparticles for the improved therapeutic efficacy of all-trans-retinoic acid: A study of Acute Myeloid Leukemia (AML) cell differentiation *in vitro*. *Med. Chem.*, **2012**, *8*(5), 805-810.
<http://dx.doi.org/10.2174/157340612802084333> PMID: 22741806
- [114] Li, Y.; Qi, X.R.; Maitani, Y.; Nagai, T. PEG-PLA diblock copolymer micelle-like nanoparticles as all-trans-retinoic acid carrier: *In vitro* and *in vivo* characterizations. *Nanotechnology*, **2009**, *20*(5), 055106.
<http://dx.doi.org/10.1088/0957-4484/20/5/055106> PMID: 19417337
- [115] Miwako, I.; Kagechika, H. Tamibarotene. *Drugs Today (Barc)*, **2007**, *43*(8), 563-568.
<http://dx.doi.org/10.1358/dot.2007.43.8.1072615> PMID: 17925887
- [116] Martino, O.D.; Welch, J.S. Retinoic acid receptors in acute myeloid leukemia therapy. *Cancers (Basel)*, **2019**, *11*(12), E1915.
<http://dx.doi.org/10.3390/cancers11121915> PMID: 31805753
- [117] Hashimoto, Y.; Kagechika, H.; Kawachi, E.; Fukasawa, H.; Saito, G.; Shudo, K. Evaluation of differentiation-inducing activity of retinoids on human leukemia cell lines HL-60 and NB4. *Biol. Pharm. Bull.*, **1996**, *19*(10), 1322-1328.
<http://dx.doi.org/10.1248/bpb.19.1322> PMID: 8913505
- [118] Naina, H.V.; Levitt, D.; Vusirikala, M.; Anderson, L.D., Jr; Scaglioni, P.P.; Kirk, A.; Collins, R.H., Jr. Successful treatment of relapsed and refractory extramedullary acute promyelocytic leukemia with tamibarotene. *J. Clin. Oncol.*, **2011**, *29*(18), e534-e536.
<http://dx.doi.org/10.1200/JCO.2011.34.8953> PMID: 21482998
- [119] Takeshita, A.; Asou, N.; Atsuta, Y.; Sakura, T.; Ueda, Y.; Sawa, M.; Dobashi, N.; Taniguchi, Y.; Suzuki, R.; Nakagawa, M.; Tamaki, S.; Hagihara, M.; Fujimaki, K.; Furumaki, H.; Obata, Y.; Fujita, H.; Yanada, M.; Maeda, Y.; Usui, N.; Kobayashi, Y.; Kiyoi, H.; Ohtake, S.; Matsumura, I.; Naoe, T.; Miyazaki, Y. Tamibarotene maintenance improved relapse-free survival of acute promyelocytic leukemia: A final result of prospective, randomized, JALSG-APL204 study. *Leukemia*, **2019**, *33*(2), 358-370.
<http://dx.doi.org/10.1038/s41375-018-0233-7> PMID: 30093681
- [120] Tian, L.; Gao, J.; Yang, Z.; Zhang, Z.; Huang, G. Tamibarotene-loaded PLGA microspheres for intratumoral injection administration: Preparation and evaluation. *AAPS PharmSciTech*, **2018**, *19*(1), 275-283.
<http://dx.doi.org/10.1208/s12249-017-0827-9> PMID: 28702817
- [121] Kanai, F.; Obi, S.; Fujiyama, S.; Shiina, S.; Tamai, H.; Mochizuki, H.; Koike, Y.; Imamura, J.; Yamaguchi, T.; Saida, I.; Yokosuka, O.; Omata, M. An open-label phase I/II study of tamibarotene in patients with advanced hepatocellular carcinoma. *Hepatol. Int.*, **2014**, *8*(1), 94-103.
<http://dx.doi.org/10.1007/s12072-013-9459-7> PMID: 26202410
- [122] Yang, Y.; Gao, J.; Ma, X.; Huang, G. Inclusion complex of tamibarotene with hydroxypropyl- β -cyclodextrin: Preparation, characterization, *in-vitro* and *in-vivo* evaluation. *Asian J. Pharm. Sci.*, **2017**, *12*(2), 187-192.
- [123] Suarez, S.; O'Hara, P.; Kazantseva, M.; Newcomer, C.E.; Hopfer, R.; McMurray, D.N.; Hickey, A.J. Respirable PLGA microspheres containing rifampicin for the treatment of tuberculosis: Screening in an infectious disease model. *Pharm. Res.*, **2001**, *18*(9), 1315-1319.
<http://dx.doi.org/10.1023/A:1013094112861> PMID: 11683246
- [124] Doh, K.-O.; Yeo, Y. Application of polysaccharides for surface modification of nanomedicines. *Ther. Deliv.*, **2012**, *3*(12), 1447-1456.
<http://dx.doi.org/10.4155/tde.12.105> PMID: 23323561
- [125] Anselmo, A.C.; Mitragotri, S. Nanoparticles in the clinic: An update post COVID-19 vaccines. *Bioeng. Transl. Med.*, **2021**, *6*(3), e10246.
<http://dx.doi.org/10.1002/btm2.10246> PMID: 34514159
- [126] Darwiche, N. Epigenetic mechanisms and the hallmarks of cancer: An intimate affair. *Am. J. Cancer Res.*, **2020**, *10*(7), 1954-1978.
PMID: 32774995
- [127] Bensa, V.; Calarco, E.; Giusto, E.; Perri, P.; Corrias, M.V.; Ponzoni, M.; Brignole, C.; Pastorino, F. Retinoids delivery systems in cancer: Liposomal fenretinide for neuroectodermal-derived tumors. *Pharmaceuticals (Basel)*, **2021**, *14*(9), 854.
<http://dx.doi.org/10.3390/ph14090854> PMID: 34577553

DISCLAIMER: The above article has been published, as is, ahead-of-print, to provide early visibility but is not the final version. Major publication processes like copyediting, proofing, typesetting and further review are still to be done and may lead to changes in the final published version, if it is eventually published. All legal disclaimers that apply to the final published article also apply to this ahead-of-print version.