Concept Paper

SALIQ in Rhabdomyosarcoma: A Repurposed Multidrug Regimen to Augment Standard Treatments by Adding Simvastatin, All Trans Retinoic Acid, Lithium, Itraconazole, and Quercetin

RICHARD E. KAST * , Mohamed S. Zaghloul , Iacopo Sardi , Marc-Eric Halatsch

Posted Date: 28 September 2023

doi: 10.20944/preprints202309.1957.v1

Keywords: chemotherapy; repurposed drugs; rhabdomyosarcoma

Concept Paper

SALIQ in Rhabdomyosarcoma: A Repurposed Multidrug Regimen to Augment Standard Treatments by Adding Simvastatin, All Trans Retinoic Acid, Lithium, Itraconazole, and Quercetin

Richard E. Kast [1,*], Mohamed S. Zaghloul [2], Iacopo Sardi [3] and Marc-Eric Halatsch [4]

[1] IIAIGC Study Center, 11 Arlington Ct, Burlington, Vermont 05408 USA;
[2] Radiation Oncology Department, Children's Cancer Hospital & National Cancer Institute, Cairo University, Cairo, EGYPT; mszagh@yahoo.com
[3] Neuro-Oncology Unit, Meyer Children's Hospital IRCCS, 50139 Florence, ITALY; iacopo.sardi@meyer.it
[4] Department of Neurosurgery, Cantonal Hospital of Winterthur, 8400 Winterthur, Switzerland. marc-eric.halatsch@ksw.ch
* Correspondence: richarderickast@gmail.co

Abstract: Rhabdomyosarcoma is a cancer arising from arrested myogenic differentiation, seen mainly in children or adolescents. Metastatic rhabdomyosarcoma is often fatal even with aggressive cytotoxic chemotherapies, surgery, and irradiation. SALIQ is an acronym for a multidrug augmentation regimen designed as an adjunct to current rhabdomyosarcoma chemotherapies. SALIQ uses five common non-oncology drugs, repurposed from general medicine use, to promote malignant clone maturation and inhibit rhabdomyosarcoma growth. The five drugs are: the cholesterol lowering drug simvastatin, the acne medicine tretinoin (ATRA), the psychiatric drug lithium carbonate, the antifungal drug itraconazole, and the food supplement quercetin. All five drugs are in common use for non-cancer conditions, are cheap, have an eminently safe side effect profile, and all five have preclinical evidence and good rationale for inhibiting rhabdomyosarcoma growth.

Keywords: chemotherapy; repurposed drugs; rhabdomyosarcoma

1. Introduction

This paper introduces SALIQ, a new adjunctive multidrug regimen for treating rhabdomyosarcoma that is projected to impose a low side effect burden. SALIQ is an acronym for the regimen that uses five already marketed non-oncology drugs with well-established data showing that they can inhibit one or another of the known growth drivers active in rhabdomyosarcoma.

Rhabdomyosarcoma is mainly a childhood cancer expressing myogenic markers MyoD, myogenin, and muscle related proteins, myosin heavy chain, skeletal α-actin, and desmin [1–4]. Four basic categories are recognized - embryonal, alveolar, spindle cell/sclerosing, and pleomorphic [5]. Embryonal (e-rhabdomyosarcoma) and alveolar (a-rhabdomyosarcoma) predominate. Children presenting with metastatic rhabdomyosarcoma have a 3-year event-free survival of 30% and overall survival of 49% after standard current cytotoxic treatments [6]. Regimens from intensive chemotherapy up to high doses with stem-cell support and radiotherapy have been tested over the years to little avail [6–8]. Studies like these in widely metastatic rhabdomyosarcoma using intensive chemotherapy imposed significant side effect burdens. Therefore we are pursuing regimens that do not lower quality of life for these children. Examples of lower side effect burden regimens: low-dose continuous cytotoxic chemotherapy (daily without interruption), or non-genotoxic drugs active against specific molecular targets, or repurposed multidrug regimens like SALIQ.

 doi:10.20944/preprints202309.1957.v1

Because rhabdomyosarcoma is a cancer of defective myocyte maturation, an overarching theme of SALIQ development was to find drugs to remove blocks to myoblast maturation in rhabdomyosarcoma cells.

Rhabdomyosarcomas are histologically similar, immunohistochemical stain positive for desmin, myogenin, and MyoD but are otherwise biologically diverse [1,3,4,6]. All forms of rhabdomyosarcoma are diseases of impaired myogenic differentiation [7,8].

The approach of SALIQ was to identify the known abnormalities blocking differentiation in rhabdomyosarcoma then looking at currently marketed drugs that have data that they might be repurposed to inhibit these identified differentiation blocks. Many different forces are active in impeding differentiation of the rhabdomyosarcoma cell. Only some of these are discussed here.

Rhabdomyosarcoma's molecular classification is evolving [9]. a-rhabdomyosarcoma is more common in adolescents and carries a worse prognosis. Many variables influence 5 year survival after diagnosis - most prominently a worse prognosis if metastases are present. Many different treatment regimens have been reported over that last 2 decades using various combinations of cyclophosphamide, dactinomycin, doxorubicin, ifosfamide, radiotherapy, surgical resection, temozolomide, topotecan, vincristine, vinorelbine, and others. Yet a significant number of children still succumb to the disease.

The SALIQ drugs are: 1) the cholesterol lowering drug simvastatin, 2) all trans retinoic acid (ATRA), a vitamin A metabolite used topically in the treatment of acne, 3) the mood stabilizing drug lithium carbonate, 4) the antifungal drug itraconazole, and 5) the dietary supplement quercetin. Since quercetin is found in high amounts in onions, increased dietary intake of onions and dried onion powder are an additional option. How these drugs might impede rhabdomyosarcoma growth will be presented in section 3 below. Before that, in section 2, three core elements of rhabdomyosarcoma growth relevant to the SALIQ drugs´ actions are reviewed. See Table 1 for quick reference to these.

2. Some elements of rhabdomyosarcoma relevant to SALIQ

2. A. PAX and FOXO1

A fusion product of two transcription factors, PAX (Pax7 or Pax3) and FOXO1 is the result of a common chromosomal translocation found in 80% of a-rhabdomyosarcoma. Degree of PAX-FOXO1 expression is correlated with shorter survival [10]. a-rhabdomyosarcoma without this fusion protein clinically resembles e-rhabdomyosarcoma [11]. Both PAX and FOXO1 have an N-terminal DNA binding and a C-terminal transactivation domain. The PAX-FOXO1 fusion protein is more stable than PAX transcription factor alone. Both PAX3/PAX7 DNA binding and transcriptional activation of the fusion protein is greater than wild-type PAX proteins.The FOXO1 transactivation domain is responsible for interacting with basal transcriptional machinery in this fusion product, abnormally and excessively promoting transcription of PAX binding DNA sites (genes). The PAX fragment is selecting which genes are going to be transcriptionally upregulated by the FOXO1 transactivation domain [1,2]. An unhappy union.

PAX-FOXO1 is resistant to proteolytic degradation, is gene amplified, has increased transcription activity, and increased translation in a-rhabdomyosarcoma. Individually PAX and FOXO1 are retained in cytosol - and hence inactive - after phosphorylation by Akt. The fusion protein PAX-FOXO1 is resistant to Akt phosphorylation, hence transported to nucleus more readily than the individual components would be [2]. Pax-FOXO1 fusion proteins are resistant to Akt activity and therefore predominantly reside in the nucleus. Pax3-FOXO1 and Pax7-FOXO1 exhibit up to 100 fold greater transcriptional activity compared to wild type Pax3 and Pax7 proteins.

2. B. Glycogen synthase kinase 3b

PAX3-FOXO1 enhances glycogen synthase kinase 3beta (GSK3) transcription/translation. GSK3 is a serine-threonine kinase that is activated by its tyrosine-279/216 phosphorylation and inhibited by its phosphorylation on serine 9 [12]. The phosphatase PP2A removes GSK3's inhibiting serine 9

 doi:10.20944/preprints202309.1957.v1

phosphorylation, reactivating GSK3. PP2A activity is inversely correlated with the level of phosphorylated GSK3 in kainic acid excitotoxic mouse brain [13].

Parenthetical note: Inactive PP2A becomes activated in the presence of several common dopamine receptor 2 inhibiting antipsychotic medicines (haloperidol, paliperidone, penfluridol, perphenazine, thioridazine) [14]. Since both lithium [15,16] and phenothiazine class antipsychotic medicines [17,18] have extensive preclinical databases showing potential cancer growth inhibition, it seems they may work against each other in that role vis a vis GSK3 function. The combination might be best avoided until more is known.

GSK3 inhibition allows non phosphorylated beta-catenin's nuclear maturation functions to proceed. Beta-catenin phosphorylated by GSK3 is degraded in the proteasome. This process is depicted in Figure 1. See section 5. below on lithium for details.

GSK3 overactivity contributes to the undifferentiated, proliferative phenotype in rhabdomyosarcoma [19].

2. C. MyoD, myogenin, and myogenesis

Myogenin is a gene derepressed by the functioning transcription factor MyoD. *Myogenin*'s protein product, myogenin, is essential for myogenic differentiation [2,20,21]. Any event blocking or hindering myogenin transcription would be predicted to contribute to maintaining rhabdomyosarcoma [22].

It is probable that e-rhabdomyosarcoma results from an earlier differentiation stage than a-rhabdomyosarcoma because a-rhabdomyosarcomas express three times more myogenin than does e-rhabdomyosarcoma.

MyoD is a muscle specific transcription factor. It can induce a differentiated nonmuscle cell to redifferentiate to a myocyte without going through a pluripotent stem cell stage but cannot do this without myogenin [21]. MyoD and myogenin exist in an amplifying feedback loop maintaining each other's expression in normal skeletal muscle development and maturation [2,20,21]. Many MyoD cofactors (peptides, proteins, miRNAs, long noncoding RNAs, histone deacetylases, etc) are recognized, and potentially required, that allow or inhibit MyoD to act as a myocyte differentiation promoting transcription factor [23].

Rhabdomyosarcomas express MyoD but preliminary data indicate that these cofactors are preventing MyoD from derepressing maturation programs in rhabdomyosarcoma [2].

Forced ectopic expression of PAX/FOXO1 in murine myoblasts or satellite cells generated malignant cells similar to rhabdomyosarcoma [24]. The PAX/FOXO1 fusion protein fails to derepress *myogenin* [24].

3. Simvastatin

Simvastatin is a common cholesterol lowering medicine, widely prescribed worldwide. Simvastatin and other cholesterol lowering drugs of this class, the "statins", are 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors. They have a considerable preclinical database showing potential for cancer growth inhibition [25–30]. Clear clinical benefit from statin use has not yet been shown.

Currently marketed examples of statins are atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. Pravastatin and rosuvastatin are hydrophilic, simvastatin and atorvastatin are lipophilic [31,32]. It has been the more lipophilic statins that have shown greater preclinical potential to inhibit cancer growth [25,30].

In adults, high doses of simvastatin (~80 mg/day) carry a higher risk of muscle pain or rhabdomyolysis compared with other statins [33]. This might be a plus as well as a minus when treating rhabdomyosarcoma. This higher muscle pain with simvastatin compared to that seen with other statins may indicate that simvastatin, as a lipophilic statin, attains higher muscle tissue levels than do other statins [34].

 doi:10.20944/preprints202309.1957.v1

HMG-CoA reductase is the rate-limiting step in cholesterol synthesis, converting HMG-CoA to mevalonic acid. Simvastatin is highly lipophilic, metabolized by CYP3A4, and has a T½ of 2 hours although clinical suppression of HMG-CoA reductase is continuous [35].

Oddly, i) despite these preclinical observations of potential benefit of simvastatin, and 2) the generally benign nature of simvastatin, and 3) the serious threat to life from rhabdomyosarcoma, yet as of 2023 there has been no published clinical trial of simvastatin or any other HMG-CoA reductase inhibitor as treatment adjunct in rhabdomyosarcoma.

Proliferation and invasion of mature muscle cells, including those within the venous wall, are inhibited by lipophilic statins atorvastatin or simvastatin but not by hydrophilic statins like pravastatin [36].

HMG-CoA reductase statins also inhibit trans-prenyltransferases including geranylgeranyl pyrophosphate synthase resulting in depletion of geranylgeranyl diphosphate stores in muscle cells and rhabdomyosarcoma growth inhibition [37,38]. Simvastatin inhibits rhabdomyosarcoma cell line growth in vitro by depletion of geranylgeranyl diphosphate [38]. Lovastatin also inhibited in vitro proliferation of rhabdomyosarcoma cells [39].

It remains unproven which of the seven approved and marketed statins would be most effective as rhabdomyosarcoma treatment adjunct. Preclinical evidence would indicate simvastatin.

4. ATRA

ATRA (tretinoin is synonym) is a normal and essential metabolic product of retinoic acid forms (vitamin A) present in our food. ATRA is probably the primary biologically active form of the retinoids. It activates all three main retinoid receptors (RAR): RAR-alpha, RAR-gamma, and RXR. Vitamin A is an essential nutrient as animals cannot synthesize it [40]. ATRA drives differentiation in many different cell lineages and settings [41]. It is also used as a pharmaceutical driver of differentiation in pediatric neuroblastoma and pediatric acute promyelocytic leukemia [42–44]. ATRA has been used successfully as a differentiation inducing agent in treating selected pediatric cancers for decades [42,45,46].

Sine oculis homeobox homolog 1 (SIX1) is a transcription factor crucial in embryogenesis. SIX1 is highly expressed in rhabdomyosarcoma. SIX1 is one of the several transcription factors active in maintaining a muscle progenitor-like state in rhabdomyosarcoma. SIX1 loss induces partial differentiation of rhabdomyosarcoma cells and impedes those cells' growth in vitro [47]. SIX1 is highly overexpressed in rhabdomyosarcoma where it forms part of the myocyte maturation block [47–49]. SIX1 is upregulated, forming part of the drive to pathologic growth, invasion, and metastasis across a variety of cancers [50–53]. ATRA reduced SIX1 expression in a myoblast cell line [54].

mRNA and protein of SIX1 and its transcriptional coactivators EYA1 and EYA2 are elevated in pulmonary fibrosis. The increased SIX1 here is a reparative reactivation on a basis of chronic alveolar damage - a wound repair triggered developmental program reactivation [55].

ATRA slowed proliferation, and resulted in a more differentiated myocyte phenotype in rhabdomyosarcoma cell lines but did not effect survival in a xenograft murine rhabdomyosarcoma model [56,57]. nanoM ATRA in vitro promoted nontransformed myoblast maturation as reflected by increased cell content of myogenin, myosin heavy chain, and myocyte fusion while inhibiting proliferation [58]. ATRA promoted in vitro differentiation of a patient derived a-rhabdomyosarcoma cell line [59]. Many authors using many different rhabdomyosarcoma cell lines have shown that ATRA increased differentiation signs - myotube-like giant cell formation, increased creatinine kinase, reduced proliferation, etc [60–63]. However not all rhabdomyosarcoma cell lines are equally sensitive to ATRA mediated differentiation or proliferation inhibition [64–66].

ATRA increases rhabdomyosarcoma cell lines' synthesis and secretion of myogenin [67,68]. As discussed in section 2.C. above, myogenin is the sine qua non for muscle cell differentiation.

Rhabdomyosarcoma uses many autocrine growth signaling systems, synthesizing VEGF and expressing VEGF receptor 1 among them. Anti-VEGF monoclonal antibody slows rhabdomyosarcoma growth and forced expression of the PAX-FOXO1 fusion protein into non-malignant muscle cells, induced expression of VEGF receptor 1 [69–71]. ATRA decreased

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 28 September 2023 doi:10.20944/preprints202309.1957.v1

rhabdomyosarcoma cell growth and synthesis of VEGF. Adding exogenous VEGF rescued proliferation [71].

In vitro, 3 microM ATRA inhibited the hepatocyte growth factor (HGF) secretion from a glioblastoma cell line [72]. HGF as agonist for its cognate receptor c-Met is discussed below as a growth drive element in rhabdomyosarcoma.

A search for published research showed no clinical trial results of ATRA (tretinoin), isotretinoin, or any other retinoid in rhabdomyosarcoma.

5. Lithium

Lithium, as lithium carbonate, is commonly used in psychiatry to reduce wide mood swings where its primary locus of action is inhibition of GSK3 [73]. Lithium inhibits GSK-3 in a variety of clinical settings and diseases [74–76]. Lithium also has an extensive database on its adjunctive use in treating various cancers [77–79].

Experience with Li+ use in children is limited. Lithium has a narrow therapeutic index when treating psychiatric problems. In children weighing 20 kg to 30 kg, 600 mg to 1500 mg/day in divided doses would be a typical dose. Lithium plasma levels should be kept around 1 mEq/L Li+ until further experience might dictate other levels best. Severe side effects are seen as plasma levels approach or exceed 2 mEq/L necessitating regular Li+ blood level monitoring.

GSK3 is the central enzyme inhibited by Li+ that results in some inhibition of malignant growth [15,79,80]. As briefly presented in section 2.B. above, GSK3 is a serine/threonine kinase expressed in all mammalian cells. GSK3 is constitutively active and is negatively regulated by phosphorylation on serine-21 and/or serine-9, primarily by Akt, but also through growth factor stimulation of mitogen activated protein kinases (MAPKs), mTOR, protein kinase A (PKA), and protein kinase C (PKC).

Normal human plasma Li+ levels during psychiatric treatment are typically ~ 1mEq. In vitro cytotoxic LD50 to rhabdomyosarcoma cell lines was between 20 and 50 mM LiCl but in vitro colony suppression was 10% of controls at 10 mM LiCl [81]. Since 10 mM LiCl = about 2 mEq/L Li+ we might get only slight Li+ mediated rhabdomyosarcoma growth suppression.

Li+ stabilization of beta-catenin resulting in its enhanced nuclear signaling, induced embryonic stem cell differentiation in hemangioblast-like cells [82]. It is the intent of Li+ use in SALIQ to do the same in rhabdomyosarcoma cells. Post-natal myogenesis and myocyte maturation processes are accelerated by reduction of GSK3 activity [83,84]. A low-therapeutic (0.5 mEq) dose of Li promoted in vitro myoblast fusion and myogenic differentiation in a myoblast cell line [85].

PAX3-FOXO1 enhances GSK3 activity which in turn represses myogenesis activity. GSK3 repressed muscle creatine kinase promoter activity and hyperphosphorylated myogenin, rendering it nonfunctional in driving muscle differentiation in rhabdomyosarcoma cells [19]. Pharmacological inhibition of GSK3 rescues PAX3-FOXO1 repression of myogenesis in rhabdomyosarcoma cells [19]. This chain of events is schematically depicted in Figure 1.

GSK3 action is integral to inhibiting the WNT/β-catenin pathway. as depicted in Figure 1. Wnt signaling activity is a pro-differentiating force in normal muscle [86,87] as well as in rhabdomyosarcoma [7,88,89]. Wnt agonists decreased proliferation and promoted differentiation in a-rhabdomyosarcoma cells [90].

Again, despite the preclinical data showing Li+ induction of rhabdomyosarcoma maturation and growth suppression plus the wealth of clinical experience and ease of Li use in treating psychiatric illnesses, still as of 2023 there have been no published clinical trials of Li+ in rhabdomyosarcoma.

6. Itraconazole, and Hh

Itraconazole is a widely prescribed antifungal drug. Itraconazole is used in the treatment of glioblastoma as part of the CUSP9v3 protocol and is seeing a resurgence of interest in treating other cancers [91–93]. Itraconazole has poor solubility and erratic absorption, necessitating taking itraconazole with Coke™, lemon juice, or other low pH drink. Itraconazole is among the strongest CYP3A4 inhibitors in common use. Itraconazole 5 mg/kg/day in divided doses of an oral solution

 doi:10.20944/preprints202309.1957.v1

would be a common dose for fungal prophylaxis in children aged 2–18 years undergoing immunosuppressive cytotoxic cancer treatments [94].

Hedgehog signaling (Hh) is one of the crucial signaling systems directing embryogenesis, wound healing, bone marrow homeostasis and other physiological functions [95–97]. Itraconazole inhibits Hh function across a wide range of clinical and experimental conditions [92,93,98–101].

One could reasonably deduce that normal cells either have work around from an Hh signaling block or that itraconazole in human clinical use provides only weak Hh inhibition since even high doses of itraconazole do not result in major organ system failures.

Hh signaling engagement participates in facilitating growth and treatment resistance across a wide variety of cancers [102–107]. This is also the case in rhabdomyosarcoma [88,108–113]. Multiple interventions are being explored to add Hh signaling inhibition to current rhabdomyosarcoma treatments [110,114].

Hepatocyte growth factor (HGF) signals via its cognate receptor c-Met to stimulate growth, invasion in mature cells and is crucial during morphogenesis. HGF added to cultured rhabdomyosarcoma cells resulted in increased Hh signaling and migration while a phytochemical from ginger plants, zerumbone, decreased that HGF-Hh provoked nondirected motility [115].

7. Quercetin and onions

Quercetin is widely available as a food supplement. It is found in high amounts in a variety of vegetables, the highest amounts in onions [116]. Problems of poor solubility and strong first-pass catabolism have made human studies of quercetin's anticancer potential difficult [116]. Formulation to improve solubility and absorption are available but are largely of untested effectiveness in achieving these goals. Quercetin is FDA certified as Generally Regarded as Safe (GRAS) and as such unregulated, making pharmacological attributes of quercetin products uncertain. Although multiple quercetin cancer growth inhibiting effects have been shown in preclinical study, none have yet been shown to do so in human disease [117–120].

A quercetin with lecithin proprietary product as Quercetin Phytosome 500 mg, gave 150 ng/ml plasma level at 6 hours in healthy humans [121]. A second study in healthy humans showed ~200 ng/ml plasma Cmax [122]. If this is typical for quercetin use in humans, blood levels are unlikely to be sufficient for significant rhabdomyosarcoma inhibition. However, worth a try given quercetin's benignity.

Pannexin 1 expression is decreased in rhabdomyosarcoma, while increasing its levels decreased in vitro growth [123]. Quercetin exposure increased pannexin 1 transcription in rhabdomyosarcoma cells [124].

HGF and its receptor, c-Met's tyrosine kinase overexpression contributes to suppressing differentiation in rhabdomyosarcoma [125–129]. Quercetin binds to the ATP binding site of c-Met preventing its in vitro activation by HGF [130]. Quercetin suppressed in vitro melanoma migration by preventing HGF activation of c-Met [131].

Quercetin inhibited HGF stimulation of c-Met in a medulloblastoma cell line with an IC50 of 12 microM [132]. Prostate cancer cells exposed to quercetin had reduced c-Met and Akt phosphorylation and a lower IC50 of doxorubicin [133]. In vitro 25 microM quercetin inhibited glioblastoma cell spheroid formation and migration but c-Met inhibition might not have mediated this [134]. Quercetin had an IC50 of 35 microM to HepG2 hepatoma cells [135]. It is questionable whether this microM concentration is clinically achievable.

c-Met receptor is expressed in myogenic precursor cells, and upon signaling stimulation by its ligand, HGF induces normal myogenic precursor stem cells' proliferation and migration [136]. c-Met mRNA and protein expression was elevated in rhabdomyosarcoma, exogenous HGF increasing motility but not proliferation [137]. HGF/c-Met signaling contributes to rhabdomyosarcoma's radioresistance [138]. Rhabdomyosarcoma cells can move toward differentiation with inhibition of c-Met signaling [139].

Abnormally increased c-Met is widely expressed in rhabdomyosarcoma [140–142]. Upregulation of c-Met activity contributes to the ability to establish rhabdomyosarcoma metastases. *c-Met* becomes

 doi:10.20944/preprints202309.1957.v1

unrepressed by the rhabdomyosarcoma fusion protein PAX-FOXO1, schematically shown in Figure 1 [143–145]. Stronger c-Met expression correlates to greater rhabdomyosarcoma tissue invasion [146]. Histologically, tumors with lower c-Met expression were characterized as more mature and differentiated, suggesting that c-Met expression in rhabdomyosarcoma functions as a suppressor of differentiation.

Clinical study NCT03245151 is of a multi-tyrosine kinase inhibitor, lenvatinib, in pediatric cancers including rhabdomyosarcoma. It is underway but results as of this writing in mid-2023 are unknown. Higher HGF/c-Met signaling activity is associated with lenvatinib resistance in adult cancers [147]. This would potentially make quercetin plus lenvatinib a particularly attractive combination for rhabdomyosarcoma. Lenvatinib blood levels, and hence side effects, can be expected to increase in people on strong CYP3A4 inhibitors like itraconazole [148]. These side effects can often be treated by simple dose reduction [148].

Studies in humans show few side effects from up to 2000 mg quercetin/day. Based on that lack, clinical utility might be doubtful but the preclinical studies showing potential quercetin benefits plus the rarity of side effects make trying quercetin reasonable.

Onions contain high levels of quercetin but absorption from that source is uncertain. Increasing onion intake per individual taste would be a harmless intervention.

8. Pharmacological considerations

The estimated rank order of side effect risk of the SALIQ drugs is, lowest to highest, quercetin, simvastatin, itraconazole, lithium carbonate, ATRA. As a conservative approach, treatment initiation should be in that order and at lower doses than their target doses. Quercetin and simvastatin can be started together on day one. ATRA, Li+ and itraconazole are best started one at a time at weekly intervals. Thus after four weeks a patient will be on all five SALIQ drugs at a low starting dose, suggested doses given in Table 3. Then bring doses up to target dose in the same order. As always in these kinds of multidrug regimens, requirement for dose reductions per individual tolerance can be expected.

8. A. Simvastatin

Studies of pediatric simvastatin use in treating hyperlipidemia showed a side effect profile no different from that of placebo [149]. Being a CYP3A4 substrate, simvastatin is technically contraindicated with itraconazole. But given the likely outcome of metastatic rhabdomyosarcoma after several failed chemotherapies, a careful try of the combination with itraconazole could be considered. There are no published reports of simvastatin overdose in children or adults.

8. B. ATRA

Many potential ATRA side effects have been reported, some serious, but fatalities are rare. Alanine aminotransferase or aspartate aminotransferase elevation or headache would be the most common side effects from ATRA [150]. ATRA is strongly teratogenic so birth control must be in place as applicable.

8. C. Lithium carbonate

Li+ is usually given as lithium carbonate. Blood Li+ levels are universally available and must be done regularly during Li+ treatment. Lithium carbonate treatment of children is not common because pediatric onset manic-depression is not common. But we do have experience in pediatric lithium carbonate use that shows good tolerability in pediatric populations [151]. Thyroid function must be monitored due to Li+ potential to inhibit thyroid function.

8. D. Itraconazole

Since itraconazole is only absorbed in low pH conditions, it must be given with an acidic beverage such as lemon juice, Coke™, or similar. Proton pump inhibitors must be avoided [152,153].

 doi:10.20944/preprints202309.1957.v1

Blood levels are readily available as a standard lab test. About 4% of people on chronic itraconazole will develop a reversible elevation of hepatic function transaminases, and 1 in 9000 develop structural liver damage.

Many drugs are formally contraindicated with itraconazole due to itraconazole's strong CYP3A4 inhibition. Specifically ATRA and simvastatin are metabolized by CYP3A4 so use is formally contraindicated with itraconazole due to potential for increased blood levels. Many of the drugs listed as contraindicated can be safely used at lower doses than usual with appropriate monitoring and dose adjustment as needed. As with most of our current cytotoxic drugs the risk of serious or fatal side effects must be weighed against the potential benefits and the likelihood of death from the cancer. Greatly complicating this decision process is the unknown degree of benefit - if any - from the SALIQ adjuvant regimen. In clinical practice the combination itraconazole together with statins, including simvastatin, is used with appropriate monitoring and dose reductions [153].

8. E. Quercetin

This is predicted to be the most benign of the SALIQ drugs. There are no known side effects in human studies.

8. Discussion and Conclusions

As amply argued elsewhere, many in the oncology community believe that adding one or two drugs will not potently inhibit a currently deadly metastatic tumor like rhabdomyosarcoma [154–158]. We can not expect any one or two drugs added to current cytotoxic chemotherapies to have strong disease inhibiting effects. Aggressively growing tumors have many workarounds to any one or two growth drive blocks. For now, multidrug regimens will be required. We therefore turn to multidrug combination cancer treatments to achieve fractional cell killing or fractional growth inhibition through drug additivity, as in Palmer et al [156]. And as in Kilmister et al "...effective treatment of cancer may require a multi-target strategy with multi-step inhibition of signaling pathways...in lieu of the long-standing pursuit of a 'silver-bullet' single-target approach" [158]. And as Lindsey et al say specifically for osteosarcoma, it "continues rapidly modifying its genotype, thus making potential targeted molecular therapeutics increasingly impractical" [159].

SALIQ also follows a military principle of breaking a crucial enemy supply chain in more than one place. Both ATRA and itraconazole inhibit Hh signaling but at two different points along the Hh signaling chain [160].

There exists more growth driving systems in rhabdomyosarcoma than the ones discussed in this paper. Dozens of cofactors interact with the growth driving systems discussed here. Some of these interacting cofactors enhance, others inhibit, function of those systems. SALIQ takes aim at inhibiting some of the more important physiological growth promoting systems. There are, however, others.

The in vitro SALIQ drug levels showing rhabdomyosarcoma growth inhibition or differentiation promotion might be higher than those attainable in humans. This potential problem might be overcome as in the works of Chow et al and of Hu et al. These authors showed that using four different antihypertensive medicines each with different mechanism of action at doses too low to be effective individually, became effective when combined all four in a single tablet [161,162]. Table 4 lists the quarter doses, usual doses, and primary mechanism of action of the four antihypertension medicines combined in the quadpill of Chow et al [161]. Should the same principle hold in rhabdomyosarcoma SALIQ could be effective even if the predicted human tumor tissue levels would be lower than in vitro effective drug levels.

A caveat: when embarking on any untested treatment regimen like SALIQ, meticulous following by the treating physician is essential.

1. Frequent meetings in person with the treating physician for a standard review of systems and targeted physical exam. Weekly is a minimum during the uptitration establishment phase unless experience with a given regimen allows longer evaluation intervals.
2. Frequent blood test monitoring for bone marrow, liver and kidney function.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 28 September 2023 doi:10.20944/preprints202309.1957.v1

3. Starting with low doses, adding one drug at a time, reevaluating after several days then increasing dose as tolerated every few days until target dose met or side effects dictate a lower dose.
4. Patients must have 24/7 ready direct access to the treating physician by phone.
5. Careful attention required to assure patient is taking medicines as directed. People often have trouble keeping these multidrug regimens and the frequent dose changes straight.
6. Once stability of dose of all drugs and tolerability established, monthly meetings will suffice.
7. When these conditions cannot be met, use of multidrug regimens like SALIQ or CUSP9v3 is not recommended until wider experiences with them can determine more suited monitoring recommendations.

These seven recommendations all stem from a basic principle of combat, whether it is fencing, chess, go, or actual warfare. General and warfare theorist Carl von Clausewitz (1780-1831) expressed it as "Every plan which enters too much into the detail of the course of the combat is therefore faulty and ruinous, for detail does not depend merely on general grounds, but on other particulars which it is impossible to know beforehand." General and later President of the USA Dwight D. Eisenhower (1890-1969) said it this way: "In preparing for battle I have always found that plans are useless, but planning is indispensable.". These military aphorisms express rules for effective practice of medicine too and are particularly applicable for SALIQ use.

The five drugs of SALIQ might not be the ideal drugs to inhibit the relevant growth and treatment resistance pathways active in rhabdomyosarcoma, but these are the drugs we have today in 2023. Given the likely unfavorable outcome once a rhabdomyosarcoma has widely metastasized plus the expected benign nature of adding the SALIQ drugs to standard treatments, the risk/potential benefit is well worth pilot study.

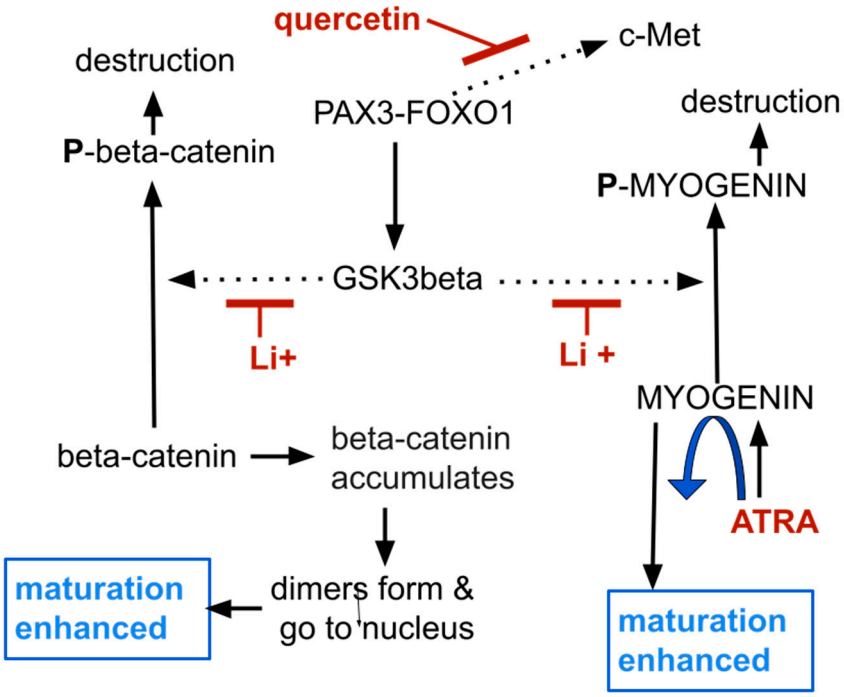

Figure 1. Schematic showing relationship between pathologic fusion protein PAX-FOXO1 and several intracellular physiological changes consequent to that. See text for details and references. Omitted are many cofactors that interact with the processes shown here, some of which enhance, some of which inhibit a given reaction. Intermediate steps in these reactions are also omitted from the schematic. Dotted arrows indicate processes inhibited by the indicated drug.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 28 September 2023 doi:10.20944/preprints202309.1957.v1

Table 1. List of some rhabdomyosarcoma cells' physiological elements relevant to the SALIQ regimen.

c-MET	a tyrosine kinase stimulated by HGF, its transcription enhanced by Pax3-FOXO1
FOXO1	transcription factor directing transcription of target genes
GGD	geranylgeranyl diphosphate
GSK3	glycogen synthase kinase 1 beta, a major inhibitor of myogenesis function
HGF	hepatocyte growth factor, the cognate ligand of c-Met
Hh	Hedgehog signaling
HMG-CoA reductase	3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, a statin, the target enzyme simvastatin inhibits
MyoD	transcription factor for myocyte differentiation
myogenesis	transcription factor necessary for myocyte maturation.
Pannexin 1	an ion channel with lower function in rhabdomyosarcoma
PAX	paired box transcription factor, PAX3 or PAX7, protein transcription factor
PAX-FOXO1	PAX3-FOXO1 or PAX7-FOXO1, common abnormal fusion protein driver in rhabdomyosarcoma

Table 2. Overview of the SALIQ drugs. APL, acute promyelocytic leukemia; BSA, body surface area; ped, pediatric.

drug	ped dose	comments
simvastatin	10 to 40 mg/d	0.1% rhabdomyolysis risk over 4 years, CYP3A4 metabolism
ATRA	7 mg/m²/BSA bid	is 30% of standard ATRA ped APL dose, CYP3A4 metabolism
lithium carbonate	300-600 mg/d	little experience with Li+ in children, renal elimination
itraconazole	5 mg/kg/day	strong CYP3A4 inhibition
quercetin	1 to 2 g/d	potentially ineffective

Table 3. Suggested starting order, doses, and uptitration schedule. * This cannot be predicted due to strong CYP3A4 inhibition by itraconazole. Doses can be titrated by careful monitoring. ** Blood monitoring required, dose adjusted to target blood level of 1 mEq/L. Recommended starting order - quercetin, simvastatin, itraconazole, lithium carbonate, ATRA. Note that simvastatin with itraconazole is contraindicated due to potential for increased simvastatin levels. These doses are for older children and teenagers. Dose reductions to tolerability can be expected.

drug	starting dose	target dose
simvastatin	10 mg/day	20 to 40 mg/day
ATRA	7 mg/m²/BSA bid	cannot be predicted *
lithium carbonate	300 mg/day	600 mg/day **
itraconazole	2.5 mg/kg/day	5 mg/kg/day
quercetin	O.5 g/day	2 g/day

Table 4. Data from Chow et al, ref. 161 showing quadpill dose with percent of common human dose in treating hypertension. ARB, angiotensin receptor blocker. MOA = primary mechanism of blood pressure lowering action.

drug	quadpill dose/d (%)	Common dose/d	MOA
irbesartan	37·5 mg (25%)	150 mg	ARB
amlodipine	1·25 mg (25%)	5 mg	Ca++ channel blocker
indapamide	0·625 mg (25%)	2.5 mg	thiazide diuretic
bisoprolol	2·5 mg (25%)	10 mg	beta blocker

Abbreviations

All trans retinoic acid (ATRA); glycogen synthase kinase 3beta (GSK3); hepatocyte growth factor (HGF); 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA); retinoid receptors (RAR); Sine oculis homeobox homolog 1 (SIX1);

References

1. Hettmer S, Linardic CM, Kelsey A, Rudzinski ER, Vokuhl C, Selfe J, Ruhen O, Shern JF, Khan J, Kovach AR, Lupo PJ, Gatz SA, Schäfer BW, Volchenboum S, Minard-Colin V, Koscielniak E, Hawkins DS, Bisogno G, Sparber-Sauer M, Venkatramani R, Merks JHM, Shipley J. Molecular testing of rhabdomyosarcoma in clinical trials to improve risk stratification and outcome: A consensus view from European paediatric Soft tissue sarcoma Study Group, Children's Oncology Group and Cooperative Weichteilsarkom-Studiengruppe. Eur J Cancer. 2022;172:367-386. doi:10.1016/j.ejca.2022.05.036.
2. Keller C, Guttridge DC. Mechanisms of impaired differentiation in rhabdomyosarcoma. FEBS J. 2013;280(17):4323-34. doi:10.1111/febs.12421.
3. Gallego Melcón S, Sánchez de Toledo Codina J. Molecular biology of rhabdomyosarcoma. Clin Transl Oncol. 2007;9(7):415-9. doi:10.1007/s12094-007-0079-3.
4. Xia SJ, Pressey JG, Barr FG. Molecular pathogenesis of rhabdomyosarcoma. Cancer Biol Ther. 2002;1(2):97-104. doi:10.4161/cbt.51.
5. Leiner J, Le Loarer F. The current landscape of rhabdomyosarcomas: an update. Virchows Arch. 2020;476(1):97-108. doi:10.1007/s00428-019-02676-9.
6. Parham DM, Giannikopoulos P. Rhabdomyosarcoma: From Obscurity to Clarity in Diagnosis … But With Ongoing Challenges in Management: The Farber-Landing Lecture of 2020. Pediatr Dev Pathol. 2021;24(2):87-95. doi:10.1177/1093526620977720.
7. Yu PY, Guttridge DC. Dysregulated Myogenesis in Rhabdomyosarcoma. Curr Top Dev Biol. 2018;126:285-297. doi:10.1016/bs.ctdb.2017.10.007.
8. Pomella S, Danielli SG, Alaggio R, Breunis WB, Hamed E, Selfe J, Wachtel M, Walters ZS, Schäfer BW, Rota R, Shipley JM, Hettmer S. Genomic and Epigenetic Changes Drive Aberrant Skeletal Muscle Differentiation in Rhabdomyosarcoma. Cancers (Basel). 2023;15(10):2823. doi:10.3390/cancers15102823.
9. Agaram NP. Evolving classification of rhabdomyosarcoma. Histopathology. 2022;80(1):98-108. doi:10.1111/his.14449.
10. Skapek SX, Anderson J, Barr FG, Bridge JA, Gastier-Foster JM, Parham DM, Rudzinski ER, Triche T, Hawkins DS. PAX-FOXO1 fusion status drives unfavorable outcome for children with rhabdomyosarcoma: a children's oncology group report. Pediatr Blood Cancer. 2013;60(9):1411-7. doi:10.1002/pbc.24532.
11. Williamson D, Missiaglia E, de Reyniès A, Pierron G, Thuille B, Palenzuela G, Thway K, Orbach D, Laé M, Fréneaux P, Pritchard-Jones K, Oberlin O, Shipley J, Delattre O. Fusion gene-negative alveolar rhabdomyosarcoma is clinically and molecularly indistinguishable from embryonal rhabdomyosarcoma. J Clin Oncol. 2010;28(13):2151-8. doi:10.1200/JCO.2009.26.3814.
12. Wang Y, Yang R, Gu J, Yin X, Jin N, Xie S, Wang Y, Chang H, Qian W, Shi J, Iqbal K, Gong CX, Cheng C, Liu F. Cross talk between PI3K-AKT-GSK-3β and PP2A pathways determines tau hyperphosphorylation. Neurobiol Aging. 2015;36(1):188-200. doi:10.1016/j.neurobiolaging.2014.07.035.
13. Chu D, Tan J, Xie S, Jin N, Yin X, Gong CX, Iqbal K, Liu F. GSK-3β is Dephosphorylated by PP2A in a Leu309 Methylation Independent Manner. J Alzheimers Dis. 2016;49(2):365-75. doi:10.3233/JAD-150497.
14. O'Connor CM, Perl A, Leonard D, Sangodkar J, Narla G. Therapeutic targeting of PP2A. Int J Biochem Cell Biol. 2018;96:182-193. doi:10.1016/j.biocel.2017.10.008.
15. Snitow ME, Bhansali RS, Klein PS. Lithium and Therapeutic Targeting of GSK-3. Cells. 2021;10(2):255. doi:10.3390/cells10020255.
16. Villegas-Vázquez EY, Quintas-Granados LI, Cortés H, González-Del Carmen M, Leyva-Gómez G, Rodríguez-Morales M, Bustamante-Montes LP, Silva-Adaya D, Pérez-Plasencia C, Jacobo-Herrera N, Reyes-Hernández OD, Figueroa-González G. Lithium: A Promising Anticancer Agent. Life (Basel). 2023;13(2):537. doi:10.3390/life13020537.
17. Manoharan GB, Okutachi S, Abankwa D. Potential of phenothiazines to synergistically block calmodulin and reactivate PP2A in cancer cells. PLoS One. 2022;17(5):e0268635. doi:10.1371/journal.pone.0268635.
18. Chien W, Sun QY, Lee KL, Ding LW, Wuensche P, Torres-Fernandez LA, Tan SZ, Tokatly I, Zaiden N, Poellinger L, Mori S, Yang H, Tyner JW, Koeffler HP. Activation of protein phosphatase 2A tumor suppressor as potential treatment of pancreatic cancer. Mol Oncol. 2015;9(4):889-905. doi:10.1016/j.molonc.2015.01.002.
19. Dionyssiou MG, Ehyai S, Avrutin E, Connor MK, McDermott JC. Glycogen synthase kinase 3β represses myogenesis function in alveolar rhabdomyosarcoma. Cell Death Dis. 2014;5(2):e1094. doi:10.1038/cddis.2014.58.

20. Myer A, Olson EN, Klein WH. MyoD cannot compensate for the absence of myogenin during skeletal muscle differentiation in murine embryonic stem cells. Dev Biol. 2001;229(2):340-50. doi:10.1006/dbio.2000.9985.
21. Adhikari A, Kim W, Davie J. Myogenin is required for assembly of the transcription machinery on muscle genes during skeletal muscle differentiation. PLoS One. 2021;16(1):e0245618. doi:10.1371/journal.pone.0245618.
22. Sebire NJ, Malone M. Myogenin and MyoD1 expression in paediatric rhabdomyosarcomas. J Clin Pathol. 2003;56(6):412-6. doi:10.1136/jcp.56.6.412.
23. Battistelli C, Garbo S, Maione R. MyoD-Induced Trans-Differentiation: A Paradigm for Dissecting the Molecular Mechanisms of Cell Commitment, Differentiation and Reprogramming. Cells. 2022;11(21):3435. doi:10.3390/cells11213435.
24. Calhabeu F, Hayashi S, Morgan JE, Relaix F, Zammit PS. Alveolar rhabdomyosarcoma-associated proteins PAX3/FOXO1A and PAX7/FOXO1A suppress the transcriptional activity of MyoD-target genes in muscle stem cells. Oncogene. 2013;32(5):651-62. doi:10.1038/onc.2012.73.
25. Jiang W, Hu JW, He XR, Jin WL, He XY. Statins: a repurposed drug to fight cancer. J Exp Clin Cancer Res. 2021;40(1):241. doi:10.1186/s13046-021-02041-2.
26. Wang KH, Liu CH, Ding DC. Statins as Repurposed Drugs in Gynecological Cancer: A Review. Int J Mol Sci. 2022;23(22):13937. doi:10.3390/ijms232213937.
27. Zhu PF, Wang MX, Chen ZL, Yang L. Targeting the Tumor Microenvironment: A Literature Review of the Novel Anti-Tumor Mechanism of Statins. Front Oncol. 2021;11:761107. doi:10.3389/fonc.2021.761107.
28. Xie L, Zhu G, Shang J, Chen X, Zhang C, Ji X, Zhang Q, Wei Y. An overview on the biological activity and anti-cancer mechanism of lovastatin. Cell Signal. 2021;87:110122. doi:10.1016/j.cellsig.2021.110122.
29. Duarte JA, de Barros ALB, Leite EA. The potential use of simvastatin for cancer treatment: A review. Biomed Pharmacother. 2021;141:111858. doi:10.1016/j.biopha.2021.111858.
30. Joharatnam-Hogan N, Alexandre L, Yarmolinsky J, Lake B, Capps N, Martin RM, Ring A, Cafferty F, Langley RE. Statins as Potential Chemoprevention or Therapeutic Agents in Cancer: a Model for Evaluating Repurposed Drugs. Curr Oncol Rep. 2021;23(3):29. doi:10.1007/s11912-021-01023-z.
31. Hamelin BA, Turgeon J. Hydrophilicity/lipophilicity: relevance for the pharmacology and clinical effects of HMG-CoA reductase inhibitors. Trends Pharmacol Sci. 1998;19(1):26-37. doi:10.1016/s0165-6147(97)01147-4.
32. Vuu YM, Kadar Shahib A, Rastegar M. The Potential Therapeutic Application of Simvastatin for Brain Complications and Mechanisms of Action. Pharmaceuticals (Basel). 2023;16(7):914. doi:10.3390/ph16070914.
33. Backes JM, Howard PA, Ruisinger JF, Moriarty PM. Does simvastatin cause more myotoxicity compared with other statins? Ann Pharmacother. 2009;43(12):2012-20. doi:10.1345/aph.1M410.
34. Jamal SM, Eisenberg MJ, Christopoulos S. Rhabdomyolysis associated with hydroxymethylglutaryl-coenzyme A reductase inhibitors. Am Heart J. 2004;147(6):956-65. doi:10.1016/j.ahj.2003.12.037.
35. Pedersen TR, Tobert JA. Simvastatin: a review. Expert Opin Pharmacother. 2004;5(12):2583-96. doi:10.1517/14656566.5.12.2583.
36. Turner NA, Midgley L, O'Regan DJ, Porter KE. Comparison of the efficacies of five different statins on inhibition of human saphenous vein smooth muscle cell proliferation and invasion. J Cardiovasc Pharmacol. 2007;50(4):458-61. doi:10.1097/FJC.0b013e318123767f.
37. Araki M, Motojima K. Hydrophobic statins induce autophagy in cultured human rhabdomyosarcoma cells. Biochem Biophys Res Commun. 2008;367(2):462-7. doi:10.1016/j.bbrc.2007.12.166.
38. Araki M, Maeda M, Motojima K. Hydrophobic statins induce autophagy and cell death in human rhabdomyosarcoma cells by depleting geranylgeranyl diphosphate. Eur J Pharmacol. 2012;674(2-3):95-103. doi:10.1016/j.ejphar.2011.10.044.
39. Codenotti S, Zizioli D, Mignani L, Rezzola S, Tabellini G, Parolini S, Giacomini A, Asperti M, Poli M, Mandracchia D, Vezzoli M, Bernardi S, Russo D, Mitola S, Monti E, Triggiani L, Tomasini D, Gastaldello S, Cassandri M, Rota R, Marampon F, Fanzani A. Hyperactive Akt1 Signaling Increases Tumor Progression and DNA Repair in Embryonal Rhabdomyosarcoma RD Line and Confers Susceptibility to Glycolysis and Mevalonate Pathway Inhibitors. Cells. 2022;11(18):2859. doi:10.3390/cells11182859.
40. Liang C, Qiao G, Liu Y, Tian L, Hui N, Li J, Ma Y, Li H, Zhao Q, Cao W, Liu H, Ren X. Overview of all-trans-retinoic acid (ATRA) and its analogues: Structures, activities, and mechanisms in acute promyelocytic leukaemia. Eur J Med Chem. 2021;220:113451. doi:10.1016/j.ejmech.2021.113451.
41. Brown G. Retinoic acid receptor regulation of decision making for cell differentiation. Front Cell Dev Biol. 2023;11:1182204. doi:10.3389/fcell.2023.1182204.
42. Reynolds CP, Matthay KK, Villablanca JG, Maurer BJ. Retinoid therapy of high-risk neuroblastoma. Cancer Lett. 2003;197(1-2):185-92. doi:10.1016/s0304-3835(03)00108-3.

43. Giuli MV, Hanieh PN, Giuliani E, Rinaldi F, Marianecci C, Screpanti I, Checquolo S, Carafa M. Current Trends in ATRA Delivery for Cancer Therapy. Pharmaceutics. 2020;12(8):707. doi:10.3390/pharmaceutics12080707.
44. Masetti R, Biagi C, Zama D, Vendemini F, Martoni A, Morello W, Gasperini P, Pession A. Retinoids in pediatric onco-hematology: the model of acute promyelocytic leukemia and neuroblastoma. Adv Ther. 2012;29(9):747-62. doi:10.1007/s12325-012-0047-3.
45. Ni X, Hu G, Cai X. The success and the challenge of all trans retinoic acid in the treatment of cancer. Crit Rev Food Sci Nutr. 2019;59(sup1):S71-S80. doi:10.1080/10408398.2018.1509201.
46. Calleja EM, Warrell RP Jr. Differentiating agents in pediatric malignancies: all-trans-retinoic acid and arsenic in acute promyelocytic leukemia. Curr Oncol Rep. 2000;2(6):519-23. doi:10.1007/s11912-000-0105-x.
47. Hsu JY, Danis EP, Nance S, O'Brien JH, Gustafson AL, Wessells VM, Goodspeed AE, Talbot JC, Amacher SL, Jedlicka P, Black JC, Costello JC, Durbin AD, Artinger KB, Ford HL. SIX1 reprograms myogenic transcription factors to maintain the rhabdomyosarcoma undifferentiated state. Cell Rep. 2022;38(5):110323. doi:10.1016/j.celrep.2022.110323.
48. Yu Y, Khan J, Khanna C, Helman L, Meltzer PS, Merlino G. Expression profiling identifies the cytoskeletal organizer ezrin and the developmental homeoprotein Six-1 as key metastatic regulators. Nat Med. 2004;10(2):175-81. doi:10.1038/nm966.
49. Ehinger D, Frostberg H, Larsson S, Gisselsson D. SIX1 as a Novel Immunohistochemical Marker in the Differential Diagnosis of Rhabdomyosarcoma. Fetal Pediatr Pathol. 2023:1-12. doi:10.1080/15513815.2023.2214806.
50. Zhu G, Liu Y, Zhao L, Lin Z, Piao Y. The Significance of SIX1 as a Prognostic Biomarker for Survival Outcome in Various Cancer Patients: A Systematic Review and Meta-Analysis. Front Oncol. 2021;11:622331. doi:10.3389/fonc.2021.622331.
51. Huang S, Lin W, Wang L, Gao Y, Yuan X, Zhang P, Chen Y, Chu Q. SIX1 Predicts Poor Prognosis and Facilitates the Progression of Non-small Lung Cancer via Activating the Notch Signaling Pathway. J Cancer. 2022;13(2):527-540. doi:10.7150/jca.61385.
52. Zhao Q, Chen G, Yang X, Wang T, Yuan S, Meng Q. SIX1: A Prognostic Biomarker in Uterine Corpus Endometrial Carcinoma. Comb Chem High Throughput Screen. 2023;26(2):330-338. doi:10.2174/1386207325666220404121856.
53. Zou J, Huang Y, Chen Y, Wu Z, Xie H, Zhou H, Xing C. FOXC2 induced circCASK aggravates colorectal cancer progression by upregulating SIX1 expression. IUBMB Life. 2023 Mar 24. doi:10.1002/iub.2718.
54. Adachi Y, Masuda M, Sakakibara I, Uchida T, Niida Y, Mori Y, Kamei Y, Okumura Y, Ohminami H, Ohnishi K, Yamanaka-Okumura H, Nikawa T, Taketani Y. All-trans retinoic acid changes muscle fiber type via increasing GADD34 dependent on MAPK signal. Life Sci Alliance. 2022;5(7):e202101345. doi:10.26508/lsa.202101345.
55. Wilson C, Mertens TC, Shivshankar P, Bi W, Collum SD, Wareing N, Ko J, Weng T, Naikawadi RP, Wolters PJ, Maire P, Jyothula SS, Thandavarayan RA, Ren D, Elrod ND, Wagner EJ, Huang HJ, Dickey BF, Ford HL, Karmouty-Quintana H. Sine oculis homeobox homolog 1 plays a critical role in pulmonary fibrosis. JCI Insight. 2022;7(10):e142984. doi:10.1172/jci.insight.142984.
56. Ohi S. Characterization, anticancer drug susceptibility and atRA-induced growth inhibition of a novel cell line (HUMEMS) established from pleural effusion of alveolar rhabdomyosarcoma of breast tissue. Hum Cell. 2007;20(2):39-51. doi:10.1111/j.1749-0774.2007.00029.x.
57. Al-Tahan A, Sarkis O, Harajly M, Baghdadi OK, Zibara K, Boulos F, Dighe D, Kregel S, Bazarbachi A, El-Sabban M, Skapek SX, Saab R. Retinoic acid fails to induce cell cycle arrest with myogenic differentiation in rhabdomyosarcoma. Pediatr Blood Cancer. 2012;58(6):877-84. doi:10.1002/pbc.23246.
58. Li Q, Zhang T, Zhang R, Qin X, Zhao J. All-trans retinoic acid regulates sheep primary myoblast proliferation and differentiation in vitro. Domest Anim Endocrinol. 2020;71:106394. doi:10.1016/j.domaniend.2019.106394.
59. Ogose A, Motoyama T, Hotta T, Watanabe H. In vitro differentiation and proliferation in a newly established human rhabdomyosarcoma cell line. Virchows Arch. 1995;426(4):385-91. doi:10.1007/BF00191348.
60. Ramp U, Gerharz CD, Doehmer J, Oster O, Gabbert HE. Uniform response of c-raf expression to differentiation induction and inhibition of proliferation in a rat rhabdomyosarcoma cell line. Virchows Arch B Cell Pathol Incl Mol Pathol. 1990;59(5):271-80. doi:10.1007/BF02899414.
61. Gerharz CD, Bracke ME, Mareel MM, Gabbert HE. Modulation of invasive potential in different clonal subpopulations of a rat rhabdomyosarcoma cell line (BA-HAN-1) by differentiation induction. Clin Exp Metastasis. 1993;11(1):55-67. doi:10.1007/BF00880066.
62. Górski GK, McMorrow LE, Donaldson MH. Synergistic inhibition of human rhabdomyosarcoma cells by sodium phenylacetate and tretinoin. In Vitro Cell Dev Biol. 1993;29A(3 Pt 1):189-91. doi:10.1007/BF02634180.

63. Gabbert HE, Gerharz CD, Biesalski HK, Engers R, Luley C. Terminal differentiation and growth inhibition of a rat rhabdomyosarcoma cell line (BA-HAN-1C) in vitro after exposure to retinoic acid. Cancer Res. 1988;48(18):5264-9.
64. Ricaud S, Vernus B, Bonnieu A. Response of human rhabdomyosarcoma cell lines to retinoic acid: relationship with induction of differentiation and retinoic acid sensitivity. Exp Cell Res. 2005;311(2):192-204. doi:10.1016/j.yexcr.2005.09.011.
65. Barlow JW, Wiley JC, Mous M, Narendran A, Gee MF, Goldberg M, Sexsmith E, Malkin D. Differentiation of rhabdomyosarcoma cell lines using retinoic acid. Pediatr Blood Cancer. 2006;47(6):773-84. doi:10.1002/pbc.20650.
66. Palomares T, Castro B, del Olmo M, Iglesias A, Bilbao P, Alonso-Varona A. Influence of the level of gamma-glutamyl transpeptidase activity on the response of poorly and moderately differentiated rhabdomyosarcoma cell lines to all-trans-retinoic acid. Anticancer Drugs. 2006;17(10):1127-39. doi:10.1097/01.cad.0000236308.27962.65.
67. Arnold HH, Gerharz CD, Gabbert HE, Salminen A. Retinoic acid induces myogenin synthesis and myogenic differentiation in the rat rhabdomyosarcoma cell line BA-Han-1C. J Cell Biol. 1992;118(4):877-87. doi:10.1083/jcb.118.4.877.
68. Arnold HH, Braun T, Bober E, Buchberger A, Winter B, Salminen A. Regulation of myogenin expression in normal and transformed myogenic cell lines. Symp Soc Exp Biol. 1992;46:37-51.
69. Crouch GD, Helman LJ. All-trans-retinoic acid inhibits the growth of human rhabdomyosarcoma cell lines. Cancer Res. 1991;51(18):4882-7.
70. Miyoshi K, Kohashi K, Fushimi F, Yamamoto H, Kishimoto J, Taguchi T, Iwamoto Y, Oda Y. Close correlation between CXCR4 and VEGF expression and frequent CXCR7 expression in rhabdomyosarcoma. Hum Pathol. 2014;45(9):1900-9. doi:10.1016/j.humpath.2014.05.012.
71. Gee MF, Tsuchida R, Eichler-Jonsson C, Das B, Baruchel S, Malkin D. Vascular endothelial growth factor acts in an autocrine manner in rhabdomyosarcoma cell lines and can be inhibited with all-trans-retinoic acid. Oncogene. 2005;24(54):8025-37. doi:10.1038/sj.onc.1208939.
72. Chattopadhyay N, Butters RR, Brown EM. Agonists of the retinoic acid- and retinoid X-receptors inhibit hepatocyte growth factor secretion and expression in U87 human astrocytoma cells. Brain Res Mol Brain Res. 2001;87(1):100-8. doi:10.1016/s0165-3806(00)00154-1.
73. Dandekar MP, Valvassori SS, Dal-Pont GC, Quevedo J. Glycogen Synthase Kinase-3β as a Putative Therapeutic Target for Bipolar Disorder. Curr Drug Metab. 2018;19(8):663-673. doi:10.2174/1389200219666171227203737.
74. Malhi GS, Outhred T. Therapeutic Mechanisms of Lithium in Bipolar Disorder: Recent Advances and Current Understanding. CNS Drugs. 2016;30(10):931-49.doi:10.1007/s40263-016-0380-1.
75. Singh A, Kumar T, Velagala VR, Thakre S, Joshi A. The Actions of Lithium on Glaucoma and Other Senile Neurodegenerative Diseases Through GSK-3 Inhibition: A Narrative Review. Cureus. 2022;14(8):e28265. doi:10.7759/cureus.28265.
76. Chatterjee D, Beaulieu JM. Inhibition of glycogen synthase kinase 3 by lithium, a mechanism in search of specificity. Front Mol Neurosci. 2022;15:1028963. doi:10.3389/fnmol.2022.1028963.
77. Bilir A, Aynacioglu AS, Tuna MY. The Possible Interactions and Therapeutic Roles of Lithium Chloride and Midkine on Cancer Treatment. Crit Rev Oncog. 2019;24(1):35-45. doi:10.1615/CritRevOncog.2018029410.
78. Yang C, Zhu B, Zhan M, Hua ZC. Lithium in Cancer Therapy: Friend or Foe? Cancers (Basel). 2023;15(4):1095. doi:10.3390/cancers15041095.
79. Neofytou C, Backlund A, Blomgren K, Hermanson O. Irradiation and lithium treatment alter the global DNA methylation pattern and gene expression underlying a shift from gliogenesis towards neurogenesis in human neural progenitors. Transl Psychiatry. 2023;13(1):258. doi:10.1038/s41398-023-02560-w.
80. Natale G, Fini E, Calabrò PF, Carli M, Scarselli M, Bocci G. Valproate and lithium: Old drugs for new pharmacological approaches in brain tumors? Cancer Lett. 2023;560:216125. doi:10.1016/j.canlet.2023.216125.
81. Schleicher SB, Zaborski JJ, Riester R, Zenkner N, Handgretinger R, Kluba T, Traub F, Boehme KA. Combined application of arsenic trioxide and lithium chloride augments viability reduction and apoptosis induction in human rhabdomyosarcoma cell lines. PLoS One. 2017;12(6):e0178857. doi:10.1371/journal.pone.0178857.
82. Mnatsakanyan H, Salmeron-Sanchez M, Rico P. Lithium Directs Embryonic Stem Cell Differentiation Into Hemangioblast-Like Cells. Adv Biol (Weinh). 2021;5(8):e2000569. doi:10.1002/adbi.202000569.
83. Pansters NA, Schols AM, Verhees KJ, de Theije CC, Snepvangers FJ, Kelders MC, Ubags ND, Haegens A, Langen RC. Muscle-specific GSK-3β ablation accelerates regeneration of disuse-atrophied skeletal muscle. Biochim Biophys Acta. 2015;1852(3):490-506. doi:10.1016/j.bbadis.2014.12.006.

84. Theeuwes WF, Gosker HR, Langen RCJ, Pansters NAM, Schols AMWJ, Remels AHV. Inactivation of glycogen synthase kinase 3β (GSK-3β) enhances mitochondrial biogenesis during myogenesis. Biochim Biophys Acta Mol Basis Dis. 2018;1864(9 Pt B):2913-2926. doi:10.1016/j.bbadis.2018.06.002.
85. Kurgan N, Whitley KC, Maddalena LA, Moradi F, Stoikos J, Hamstra SI, Rubie EA, Kumar M, Roy BD, Woodgett JR, Stuart JA, Fajardo VA. A Low-Therapeutic Dose of Lithium Inhibits GSK3 and Enhances Myoblast Fusion in C2C12 Cells. Cells. 2019;8(11):1340. doi:10.3390/cells8111340.
86. Girardi F, Le Grand F. Wnt Signaling in Skeletal Muscle Development and Regeneration. Prog Mol Biol Transl Sci. 2018;153:157-179. doi:10.1016/bs.pmbts.2017.11.026.
87. De-Paula VJ, Dos Santos CCC, Luque MCA, Ali TM, Kalil JE, Forlenza OV, Cunha-Neto E. Acute and chronic lithium treatment increases Wnt/β-catenin transcripts in cortical and hippocampal tissue at therapeutic concentrations in mice. Metab Brain Dis. 2021;36(1):193-197. doi:10.1007/s11011-020-00638-8.
88. Ramadan F, Fahs A, Ghayad SE, Saab R. Signaling pathways in Rhabdomyosarcoma invasion and metastasis. Cancer Metastasis Rev. 2020;39(1):287-301. doi:10.1007/s10555-020-09860-3.
89. Chen E. Wnt Signaling in Rhabdomyosarcoma - A Potential Targeted Therapy Option. Curr Drug Targets. 2016;17(11):1245-51. doi:10.2174/1389450116666150630110625.
90. Annavarapu SR, Cialfi S, Dominici C, Kokai GK, Uccini S, Ceccarelli S, McDowell HP, Helliwell TR. Characterization of Wnt/β-catenin signaling in rhabdomyosarcoma. Lab Invest. 2013;93(10):1090-9. doi:10.1038/labinvest.2013.97.
91. Halatsch ME, Kast RE, Karpel-Massler G, Mayer B, Zolk O, Schmitz B, Scheuerle A, Maier L, Bullinger L, Mayer-Steinacker R, Schmidt C, Zeiler K, Elshaer Z, Panther P, Schmelzle B, Hallmen A, Dwucet A, Siegelin MD, Westhoff MA, Beckers K, Bouche G, Heiland T. A phase Ib/IIa trial of 9 repurposed drugs combined with temozolomide for the treatment of recurrent glioblastoma: CUSP9v3. Neurooncol Adv. 2021;3(1):vdab075. doi:10.1093/noajnl/vdab075.
92. Li CL, Fang ZX, Wu Z, Hou YY, Wu HT, Liu J. Repurposed itraconazole for use in the treatment of malignancies as a promising therapeutic strategy. Biomed Pharmacother. 2022;154:113616. doi:10.1016/j.biopha.2022.113616.
93. Wei X, Liu W, Wang JQ, Tang Z. "Hedgehog pathway": a potential target of itraconazole in the treatment of cancer. J Cancer Res Clin Oncol. 2020;146(2):297-304. doi:10.1007/s00432-019-03117-5.
94. Bury D, Tissing WJE, Muilwijk EW, Wolfs TFW, Brüggemann RJ. Clinical Pharmacokinetics of Triazoles in Pediatric Patients. Clin Pharmacokinet. 2021;60(9):1103-1147. doi:10.1007/s40262-021-00994-3.
95. Lee RT, Zhao Z, Ingham PW. Hedgehog signalling. Development. 2016;143(3):367-72. doi: 10.1242/dev.120154.
96. Wang J, Cui B, Li X, Zhao X, Huang T, Ding X. The emerging roles of Hedgehog signaling in tumor immune microenvironment. Front Oncol. 2023;13:1171418. doi:10.3389/fonc.2023.1171418.
97. Zhang Y, Beachy PA. Cellular and molecular mechanisms of Hedgehog signalling. Nat Rev Mol Cell Biol. 2023 Mar 17. doi:10.1038/s41580-023-00591-1.
98. Ban L, Mei T, Su Q, Li W, Huang Z, Liu L, Wu Y, Lv S, Wang A, Li S. Anti-fungal drug itraconazole exerts anti-cancer effects in oral squamous cell carcinoma via suppressing Hedgehog pathway. Life Sci. 2020;254:117695. doi:10.1016/j.lfs.2020.117695.
99. Deng H, Huang L, Liao Z, Liu M, Li Q, Xu R. Itraconazole inhibits the Hedgehog signaling pathway thereby inducing autophagy-mediated apoptosis of colon cancer cells. Cell Death Dis. 2020;11(7):539. doi:10.1038/s41419-020-02742-0.
100. Gerber DE, Putnam WC, Fattah FJ, Kernstine KH, Brekken RA, Pedrosa I, Skelton R, Saltarski JM, Lenkinski RE, Leff RD, Ahn C, Padmanabhan C, Chembukar V, Kasiri S, Kallem RR, Subramaniyan I, Yuan Q, Do QN, Xi Y, Reznik SI, Pelosof L, Faubert B, DeBerardinis RJ, Kim J. Concentration-dependent Early Antivascular and Antitumor Effects of Itraconazole in Non-Small Cell Lung Cancer. Clin Cancer Res. 2020;26(22):6017-6027. doi:10.1158/1078-0432.CCR-20-1916.
101. Freitas RD, Dias RB, Vidal MTA, Valverde LF, Gomes Alves Costa R, Damasceno AKA, Sales CBS, Siquara da Rocha LO, Dos Reis MG, Soares MBP, Coletta RD, Pereira TA, Bezerra DP, Gurgel Rocha CA. Inhibition of CAL27 Oral Squamous Carcinoma Cell by Targeting Hedgehog Pathway With Vismodegib or Itraconazole. Front Oncol. 2020;10:563838. doi:10.3389/fonc.2020.563838.
102. Xia R, Xu M, Yang J, Ma X. The role of Hedgehog and Notch signaling pathway in cancer. Mol Biomed. 2022;3(1):44. doi:10.1186/s43556-022-00099-8.
103. Martelli AM, Paganelli F, Truocchio S, Palumbo C, Chiarini F, McCubrey JA. Understanding the Roles of the Hedgehog Signaling Pathway during T-Cell Lymphopoiesis and in T-Cell Acute Lymphoblastic Leukemia (T-ALL). Int J Mol Sci. 2023;24(3):2962. doi:10.3390/ijms24032962.
104. Suchors C, Kim J. Canonical Hedgehog Pathway and Noncanonical GLI Transcription Factor Activation in Cancer. Cells. 2022;11(16):2523. doi:10.3390/cells11162523.
105. Tesanovic S, Krenn PW, Aberger F. Hedgehog/GLI signaling in hematopoietic development and acute myeloid leukemia-From bench to bedside. Front Cell Dev Biol. 2022;10:944760. doi:10.3389/fcell.2022.944760.

106. Meister MT, Boedicker C, Linder B, Kögel D, Klingebiel T, Fulda S. Concomitant targeting of Hedgehog signaling and MCL-1 synergistically induces cell death in Hedgehog-driven cancer cells. Cancer Lett. 2019;465:1-11. doi:10.1016/j.canlet.2019.08.012.
107. Wang H, Lai Q, Wang D, Pei J, Tian B, Gao Y, Gao Z, Xu X. Hedgehog signaling regulates the development and treatment of glioblastoma. Oncol Lett. 2022;24(3):294. doi:10.3892/ol.2022.13414.
108. Yoon JW, Lamm M, Chandler C, Iannaccone P, Walterhouse D. Up-regulation of GLI1 in vincristine-resistant rhabdomyosarcoma and Ewing sarcoma. BMC Cancer. 2020;20(1):511. doi:10.1186/s12885-020-06985-0.
109. Zarzosa P, Garcia-Gilabert L, Hladun R, Guillén G, Gallo-Oller G, Pons G, Sansa-Girona J, Segura MF, Sánchez de Toledo J, Moreno L, Gallego S, Roma J. Targeting the Hedgehog Pathway in Rhabdomyosarcoma. Cancers (Basel). 2023;15(3):727. doi:10.3390/cancers15030727.
110. Manzella G, Schäfer BW. Interfering with Hedgehog Pathway: New Avenues for Targeted Therapy in Rhabdomyosarcoma. Curr Drug Targets. 2016;17(11):1228-34. doi:10.2174/1389450116666150505122604.
111. Chelsky ZL, Paulson VA, Chen EY. Molecular analysis of 10 pleomorphic rhabdomyosarcomas reveals potential prognostic markers and druggable targets. Genes Chromosomes Cancer. 2022;61(3):138-147. doi:10.1002/gcc.23013.
112. Drummond CJ, Hanna JA, Garcia MR, Devine DJ, Heyrana AJ, Finkelstein D, Rehg JE, Hatley ME. Hedgehog Pathway Drives Fusion-Negative Rhabdomyosarcoma Initiated From Non-myogenic Endothelial Progenitors. Cancer Cell. 2018;33(1):108-124.e5. doi:10.1016/j.ccell.2017.12.001.
113. Almazán-Moga A, Zarzosa P, Molist C, Velasco P, Pyczek J, Simon-Keller K, Giralt I, Vidal I, Navarro N, Segura MF, Soriano A, Navarro S, Tirado OM, Ferreres JC, Santamaria A, Rota R, Hahn H, Sánchez de Toledo J, Roma J, Gallego S. Ligand-dependent Hedgehog pathway activation in Rhabdomyosarcoma: the oncogenic role of the ligands. Br J Cancer. 2017;117(9):1314-1325. doi:10.1038/bjc.2017.305.
114. Sun J, Lin W, Li C, Ueki H, Xue R, Sadahira T, Hu H, Wada K, Li N, Liu C, Araki M, Xu A, Huang P. Repurposing of posaconazole as a hedgehog/SMO signaling inhibitor for embryonal rhabdomyosarcoma therapy. Am J Cancer Res. 2021;11(9):4528-4540.
115. Urla C, Stagno MJ, Fuchs J, Warmann SW, Schmid E. Anticancer bioactivity of zerumbone on pediatric rhabdomyosarcoma cells. J Cancer Res Clin Oncol. 2023;149(7):3313-3323. doi:10.1007/s00432-022-04237-1.
116. Zhang Y, Fu K, Wang C, Ma C, Gong L, Zhou H, Xue X, Peng C, Li Y. Protective effects of dietary quercetin on cerebral ischemic injury: pharmacology, pharmacokinetics and bioavailability enhancing nanoformulations. Food Funct. 2023;14(10):4470-4489. doi:10.1039/d2fo03122a.
117. Lotfi N, Yousefi Z, Golabi M, Khalilian P, Ghezelbash B, Montazeri M, Shams MH, Baghbadorani PZ, Eskandari N. The potential anti-cancer effects of quercetin on blood, prostate and lung cancers: An update. Front Immunol. 2023;14:1077531. doi:10.3389/fimmu.2023.1077531.
118. Shabir I, Kumar Pandey V, Shams R, Dar AH, Dash KK, Khan SA, Bashir I, Jeevarathinam G, Rusu AV, Esatbeyoglu T, Pandiselvam R. Promising bioactive properties of quercetin for potential food applications and health benefits: A review. Front Nutr. 2022;9:999752. doi:10.3389/fnut.2022.999752.
119. Sethi G, Rath P, Chauhan A, Ranjan A, Choudhary R, Ramniwas S, Sak K, Aggarwal D, Rani I, Tuli HS. Apoptotic Mechanisms of Quercetin in Liver Cancer: Recent Trends and Advancements. Pharmaceutics. 2023;15(2):712. doi:10.3390/pharmaceutics15020712.
120. Maugeri A, Calderaro A, Patanè GT, Navarra M, Barreca D, Cirmi S, Felice MR. Targets Involved in the Anti-Cancer Activity of Quercetin in Breast, Colorectal and Liver Neoplasms. Int J Mol Sci. 2023;24(3):2952. doi:10.3390/ijms24032952.
121. Riva A, Ronchi M, Petrangolini G, Bosisio S, Allegrini P. Improved Oral Absorption of Quercetin from Quercetin Phytosome®, a New Delivery System Based on Food Grade Lecithin. Eur J Drug Metab Pharmacokinet. 2019;44(2):169-177. doi:10.1007/s13318-018-0517-3.
122. Solnier J, Chang C, Roh K, Du M, Kuo YC, BE, Hardy M, Lyon M, Gahler R. Quercetin LipoMicel—A Novel Delivery System to Enhance Bioavailability of Quercetin. J Nat Health Prod Res. 2021;3(2):1-8. doi.org/10.33211/jnhpr.17.
123. Xiang X, Langlois S, St-Pierre ME, Barré JF, Grynspan D, Purgina B, Cowan KN. Pannexin 1 inhibits rhabdomyosarcoma progression through a mechanism independent of its canonical channel function. Oncogenesis. 2018;7(11):89. doi:10.1038/s41389-018-0100-4.
124. Xiang X, Hoang HD, Gilchrist VH, Langlois S, Alain T, Cowan KN. Quercetin induces pannexin 1 expression via an alternative transcript with a translationally active 5' leader in rhabdomyosarcoma. Oncogenesis. 2022;11(1):9. doi:10.1038/s41389-022-00384-9.
125. Skrzypek K, Kusienicka A, Szewczyk B, Adamus T, Lukasiewicz E, Miekus K, Majka M. Constitutive activation of MET signaling impairs myogenic differentiation of rhabdomyosarcoma and promotes its development and progression. Oncotarget. 2015;6(31):31378-98. doi:10.18632/oncotarget.5145.
126. Du J, Wang Y, Meng L, Liu Y, Pang Y, Cui W, Zhang L, Li Z, Liu Q, Shang H, Liu C, Li F. c-MET expression potentially contributes to the poor prognosis of rhabdomyosarcoma. Int J Clin Exp Pathol. 2018;11(8):4083-4092.

127. Taulli R, Scuoppo C, Bersani F, Accornero P, Forni PE, Miretti S, Grinza A, Allegra P, Schmitt-Ney M, Crepaldi T, Ponzetto C. Validation of met as a therapeutic target in alveolar and embryonal rhabdomyosarcoma. Cancer Res. 2006;66(9):4742-9. doi:10.1158/0008-5472.CAN-05-4292.
128. Rees H, Williamson D, Papanastasiou A, Jina N, Nabarro S, Shipley J, Anderson J. The MET receptor tyrosine kinase contributes to invasive tumour growth in rhabdomyosarcomas. Growth Factors. 2006;24(3):197-208. doi:10.1080/08977190600759923.
129. Perrone C, Pomella S, Cassandri M, Pezzella M, Milano GM, Colletti M, Cossetti C, Pericoli G, Di Giannatale A, de Billy E, Vinci M, Petrini S, Marampon F, Quintarelli C, Taulli R, Roma J, Gallego S, Camero S, Mariottini P, Cervelli M, Maestro R, Miele L, De Angelis B, Locatelli F, Rota R. MET Inhibition Sensitizes Rhabdomyosarcoma Cells to NOTCH Signaling Suppression. Front Oncol. 2022;12:835642. doi:10.3389/fonc.2022.835642.
130. Baby B, Antony P, Vijayan R. Interactions of quercetin with receptor tyrosine kinases associated with human lung carcinoma. Nat Prod Res. 2018;32(24):2928-2931. doi:10.1080/14786419.2017.1385015.
131. Cao HH, Cheng CY, Su T, Fu XQ, Guo H, Li T, Tse AK, Kwan HY, Yu H, Yu ZL. Quercetin inhibits HGF/c-Met signaling and HGF-stimulated melanoma cell migration and invasion. Mol Cancer. 2015;14:103. doi:10.1186/s12943-015-0367-4.
132. Labbé D, Provençal M, Lamy S, Boivin D, Gingras D, Béliveau R. The flavonols quercetin, kaempferol, and myricetin inhibit hepatocyte growth factor-induced medulloblastoma cell migration. J Nutr. 2009;139(4):646-52. doi:10.3945/jn.108.102616.
133. Shu Y, Xie B, Liang Z, Chen J. Quercetin reverses the doxorubicin resistance of prostate cancer cells by downregulating the expression of c-met. Oncol Lett. 2018;15(2):2252-2258. doi:10.3892/ol.2017.7561.
134. Kim B, Jung N, Lee S, Sohng JK, Jung HJ. Apigenin Inhibits Cancer Stem Cell-Like Phenotypes in Human Glioblastoma Cells via Suppression of c-Met Signaling. Phytother Res. 2016;30(11):1833-1840. doi:10.1002/ptr.5689.
135. AbouAitah K, Swiderska-Sroda A, Farghali AA, Wojnarowicz J, Stefanek A, Gierlotka S, Opalinska A, Allayeh AK, Ciach T, Lojkowski W. Folic acid-conjugated mesoporous silica particles as nanocarriers of natural prodrugs for cancer targeting and antioxidant action. Oncotarget. 2018;9(41):26466-26490. doi:10.18632/oncotarget.25470.
136. Allen RE, Sheehan SM, Taylor RG, Kendall TL, Rice GM. Hepatocyte growth factor activates quiescent skeletal muscle satellite cells in vitro. J Cell Physiol. 1995;165(2):307-12. doi:10.1002/jcp.1041650211.
137. Otabe O, Kikuchi K, Tsuchiya K, Katsumi Y, Yagyu S, Miyachi M, Iehara T, Hosoi H. MET/ERK2 pathway regulates the motility of human alveolar rhabdomyosarcoma cells. Oncol Rep. 2017;37(1):98-104. doi:10.3892/or.2016.5213.
138. Jankowski K, Kucia M, Wysoczynski M, Reca R, Zhao D, Trzyna E, Trent J, Peiper S, Zembala M, Ratajczak J, Houghton P, Janowska-Wieczorek A, Ratajczak MZ. Both hepatocyte growth factor (HGF) and stromal-derived factor-1 regulate the metastatic behavior of human rhabdomyosarcoma cells, but only HGF enhances their resistance to radiochemotherapy. Cancer Res. 2003;63(22):7926-35.
139. Miekus K, Lukasiewicz E, Jarocha D, Sekula M, Drabik G, Majka M. The decreased metastatic potential of rhabdomyosarcoma cells obtained through MET receptor downregulation and the induction of differentiation. Cell Death Dis. 2013;4(1):e459. doi:10.1038/cddis.2012.199.
140. Chen Y, Takita J, Mizuguchi M, Tanaka K, Ida K, Koh K, Igarashi T, Hanada R, Tanaka Y, Park MJ, Hayashi Y. Mutation and expression analyses of the MET and CDKN2A genes in rhabdomyosarcoma with emphasis on MET overexpression. Genes Chromosomes Cancer. 2007;46(4):348-58. doi:10.1002/gcc.20416.
141. Diomedi-Camassei F, McDowell HP, De Ioris MA, Uccini S, Altavista P, Raschellà G, Vitali R, Mannarino O, De Sio L, Cozzi DA, Donfrancesco A, Inserra A, Callea F, Dominici C. Clinical significance of CXC chemokine receptor-4 and c-Met in childhood rhabdomyosarcoma. Clin Cancer Res. 2008;14(13):4119-27. doi:10.1158/1078-0432.CCR-07-4446.
142. Yan D, Dong Xda E, Chen X, Wang L, Lu C, Wang J, Qu J, Tu L. MicroRNA-1/206 targets c-Met and inhibits rhabdomyosarcoma development. J Biol Chem. 2009;284(43):29596-604. doi:10.1074/jbc.M109.020511.
143. Lukasiewicz E, Miekus K, Kijowski J, Drabik G, Wilusz M, Bobis-Wozowicz S, Majka M. Inhibition of rhabdomyosarcoma's metastatic behavior through downregulation of MET receptor signaling. Folia Histochem Cytobiol. 2009;47(3):485-9. doi:10.2478/v10042-009-0108-x.
144. Saini M, Verma A, Mathew SJ. SPRY2 is a novel MET interactor that regulates metastatic potential and differentiation in rhabdomyosarcoma. Cell Death Dis. 2018;9(2):237. doi:10.1038/s41419-018-0261-2.
145. Ginsberg JP, Davis RJ, Bennicelli JL, Nauta LE, Barr FG. Up-regulation of MET but not neural cell adhesion molecule expression by the PAX3-FKHR fusion protein in alveolar rhabdomyosarcoma. Cancer Res. 1998;58(16):3542-6.
146. Ferracini R, Olivero M, Di Renzo MF, Martano M, De Giovanni C, Nanni P, Basso G, Scotlandi K, Lollini PL, Comoglio PM. Retrogenic expression of the MET proto-oncogene correlates with the invasive phenotype of human rhabdomyosarcomas. Oncogene. 1996;12(8):1697-705.

147. Fu R, Jiang S, Li J, Chen H, Zhang X. Activation of the HGF/c-MET axis promotes lenvatinib resistance in hepatocellular carcinoma cells with high c-MET expression. Med Oncol. 2020;37(4):24. doi:10.1007/s12032-020-01350-4.
148. Hao Z, Wang P. Lenvatinib in Management of Solid Tumors. Oncologist. 2020;25(2):e302-e310. doi:10.1634/theoncologist.2019-0407.
149. Wagner J, Abdel-Rahman SM. Pediatric Statin Administration: Navigating a Frontier with Limited Data. J Pediatr Pharmacol Ther. 2016;21(5):380-403. doi:10.5863/1551-6776-21.5.380.
150. Voorberg AN, Kamphuis E, Christoffers WA, Romeijn GLE, Oosterhaven JAF, Schuttelaar MLA. Efficacy and safety of oral alitretinoin versus oral azathioprine in patients with severe chronic hand eczema: Results from a prematurely discontinued randomized controlled trial. Contact Dermatitis. 2022;87(4):366-368. doi:10.1111/cod.14161.
151. Findling RL, McNamara NK, Pavuluri M, Frazier JA, Rynn M, Scheffer R, Kafantaris V, Robb A, DelBello M, Kowatch RA, Rowles BM, Lingler J, Zhao J, Clemons T, Martz K, Anand R, Taylor-Zapata P. Lithium for the Maintenance Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled Discontinuation Study. J Am Acad Child Adolesc Psychiatry. 2019;58(2):287-296.e4. doi:10.1016/j.jaac.2018.07.901.
152. Piérard GE, Arrese JE, Piérard-Franchimont C. Itraconazole. Expert Opin Pharmacother. 2000;1(2):287-304. doi:10.1517/14656566.1.2.287.
153. Lestner J, Hope WW. Itraconazole: an update on pharmacology and clinical use for treatment of invasive and allergic fungal infections. Expert Opin Drug Metab Toxicol. 2013;9(7):911-26. doi:10.1517/17425255.2013.794785.
154. Kast RE, Alfieri A, Assi HI, Burns TC, Elyamany AM, Gonzalez-Cao M, Karpel-Massler G, Marosi C, Salacz ME, Sardi I, Van Vlierberghe P, Zaghloul MS, Halatsch ME. MDACT: A New Principle of Adjunctive Cancer Treatment Using Combinations of Multiple Repurposed Drugs, with an Example Regimen. Cancers (Basel). 2022;14(10):2563. doi:10.3390/cancers14102563.
155. Halatsch ME, Dwucet A, Schmidt CJ, Mühlnickel J, Heiland T, Zeiler K, Siegelin MD, Kast RE, Karpel-Massler G. In Vitro and Clinical Compassionate Use Experiences with the Drug-Repurposing Approach CUSP9v3 in Glioblastoma. Pharmaceuticals (Basel). 2021;14(12):1241. doi:10.3390/ph14121241.
156. Palmer AC, Chidley C, Sorger PK. A curative combination cancer therapy achieves high fractional cell killing through low cross-resistance and drug additivity. Elife. 2019;8:e50036. doi:10.7554/eLife.50036.
157. Nogales C, Mamdouh ZM, List M, Kiel C, Casas AI, Schmidt HHHW. Network pharmacology: curing causal mechanisms instead of treating symptoms. Trends Pharmacol Sci. 2022;43(2):136-150. doi:10.1016/j.tips.2021.11.004.
158. Kilmister EJ, Koh SP, Weth FR, Gray C, Tan ST. Cancer Metastasis and Treatment Resistance: Mechanistic Insights and Therapeutic Targeting of Cancer Stem Cells and the Tumor Microenvironment. Biomedicines. 2022;10(11):2988. doi:10.3390/biomedicines10112988.
159. Lindsey BA, Markel JE, Kleinerman ES. Osteosarcoma Overview. Rheumatol Ther. 2017;4(1):25-43. doi:10.1007/s40744-016-0050-2.
160. Cosio T, Di Prete M, Campione E. Arsenic Trioxide, Itraconazole, All-Trans Retinoic Acid and Nicotinamide: A Proof of Concept for Combined Treatments with Hedgehog Inhibitors in Advanced Basal Cell Carcinoma. Biomedicines. 2020;8(6):156. doi:10.3390/biomedicines8060156.
161. Chow CK, Atkins ER, Hillis GS, Nelson MR, Reid CM, Schlaich MP, Hay P, Rogers K, Billot L, Burke M, Chalmers J, Neal B, Patel A, Usherwood T, Webster R, Rodgers A; QUARTET Investigators. Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines versus standard dose monotherapy in patients with hypertension (QUARTET): a phase 3, randomised, double-blind, active-controlled trial. Lancet. 2021;398(10305):1043-1052. doi:10.1016/S0140-6736(21)01922-X.
162. Hu LX, Wang D, Liu HL, Zhang QT, Sun DS, Zhang L, Chen X, Chang GL, Wang JG. A double-blind, placebo-controlled trial on the antihypertensive treatment effect of a quadruple single-pill combination. J Clin Hypertens (Greenwich). 2021;23(4):815-822. doi:10.1111/jch.14207.