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Glycoconjugation as a promising treatment strategy for psoriasis

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Abbreviations:

HMRS, High-resolution mass spectrometry; LC, liquid chromatography; NIR, Near-Infrared Reflectance spectroscopy; NMR, Nuclear Magnetic Resonance; PASI, Psoriasis Area and Severity Index; PASI 75, Psoriasis Area and Severity Index - represents the percentage of patients who have achieved a 75% or more reduction of the score; PASI 90, Psoriasis Area and Severity Index - represents the percentage of patients who have achieved a 90% or more reduction of the score; SNAr, Aromatic nucleophilic substitution.

Abstract

Despite the progress in the development of novel treatment modalities, a significant portion of patients with psoriasis remains undertreated relative to the severity of their disease. Recent evidence points to targeting the glucose transporter GLUT1 and sugar metabolism as a novel therapeutic strategy for the treatment of psoriasis and other hyperproliferative skin diseases. In this review, we discuss glycoconjugation, an approach that facilitates the pharmacokinetics of cytotoxic molecules and ensures their preferential influx through glucose transporters. We propose pathways of glycoconjugate synthesis to increase effectiveness, cellular selectivity, and tolerability of widely-used antipsoriatic drugs. The presented approach exploiting the heightened glucose requirement of proliferating keratinocytes bears the potential to revolutionize the management of psoriasis.

Significance statement

Recent findings concerning the fundamental role of enhanced glucose metabolism and GLUT1 overexpression in the pathogenesis of psoriasis brought to light approaches that proved successful in cancer treatment. Substantial advances in the emerging field of glycoconjugation highlight the rationale for the development of glucose-conjugated antipsoriatic drugs to increase their effectiveness, cellular selectivity, and tolerability. The presented approach offers a novel therapeutic strategy for the treatment of psoriasis and other hyperproliferative skin diseases.

Keywords: psoriasis; molecular drug targeting; membrane transport; drug design

Introduction

An increasing body of evidence is accumulating suggesting a significant surge in the frequency of autoimmune diseases (AD) in the last decades (Lohi et al., 2007; Lerner and Matthias, 2015a). Psoriasis, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, inflammatory bowel diseases, and systemic lupus erythematosus are several examples (Lerner and Matthias, 2015a, 2015b). All of the mentioned conditions are a consequence of chronic activation of T and B lymphocytes in the absence of an infection or other detectable cause (Davidson and Diamond, 2001). The overall prevalence of autoimmunity is approximately 3-5% in the general population, but the effects on mortality and morbidity are significant (Jacobson et al., 1997; Eaton et al., 2007). Ironically, despite enormous advances in the molecular sciences, diagnostic methods, and clinical classification, there is still an urgent need to improve the therapeutic outcome of patients with an AD.

One of the most prevalent autoimmune diseases is psoriasis, which is a chronic inflammatory skin condition that affects 2-3% of the population worldwide (Langley et al., 2005). Symptoms of psoriasis, which include redness, scaling, flaking, pruritus, skin tightness, pain, and bleeding, have a significant impact on patients' physical and mental wellbeing (Feldman et al., 2014). Patients with psoriatic diseases can not only have skin and joint impairment but can also experience decreased quality of life and work productivity, as well as severe medical comorbidities, such as increased cardiovascular events and depression (Armstrong et al., 2013; Lebwohl et al., 2014). The dominant feature of psoriasis is an aberrant hyperproliferation of keratinocytes (Lowe et al., 2007), which are the primary cell type of the epidermis and vital participants of the immune system, recruiting T cells to the skin (Lowe et al., 2014). Activated by interleukin-12 and -23, IL-17-producing T cells (Gerosa et al., 2008) produce abundant key psoriatic cytokines such as tumor necrosis factor (TNF- α), interferon-gamma (IFN- γ), and interleukin-17 (IL-17) and -23 (IL-23), that mediate effects on keratinocytes to intensify skin inflammation (Kim and Krueger, 2015). Exaggerated proliferation of keratinocytes is a hallmark of psoriasis and results from overexpression of the previously mentioned cytokines and growth factors (Hiebert and Werner, 2018). Currently used treatment agents like calcineurin inhibitors, anti-interleukin monoclonal antibodies against proinflammatory cytokines, fumaric acid esters, glucocorticoids, retinoids, and vitamin D derivatives, tend to suppress chronic inflammation (Boehncke and Schön, 2015). Unfortunately, despite the progress in the

development of novel treatment modalities over the past decades, studies reveal that a significant proportion of patients with psoriasis remains undertreated relative to the severity of their disease (Lebwohl et al., 2014). Patients experience treatment failure with, or intolerance to, traditional systemic therapies and/or phototherapy and switch to biologic agents as second-line therapy. Side effects are the main reasons for discontinuing traditional systemic therapies, whereas lack of efficacy is the main reason for discontinuing biologic agents (Lambert et al., 2017). Biologics were reported to lose their effectiveness after long-term use (Levin et al., 2014). The toxicity of traditional compounds such as methotrexate prevents many patients from obtaining a favorable outcome from the treatment due to the development of multiple toxic effects including bone marrow suppression and gastrointestinal ulceration (Roenigk et al., 1988; Pearce and Wilson, 1996). Only 36 to 58% of patients with moderate to severe psoriasis treated according to the guidelines reach current therapeutic targets of PASI75 and PASI90, at 1 year, highlighting a gap in efficacy between selective clinical trials and the real-world setting. A population-based survey of patients, dermatologists, and rheumatologists found a high treatment dissatisfaction among the patients and a need for safe, effective, and easy-to-use therapies for psoriasis (Lebwohl et al., 2016). Thus, new, rationally designed agents are needed to replace or complement currently applied therapies. Glycoconjugation is a strategy that offers improved water solubility and stability and the potential for a selective accumulation of conjugated drugs by targeting GLUT1 receptors (Figure 1), whose expression is highly abundant in proliferating psoriatic keratinocytes (Crunkhorn, 2018). A recently published paper by Zhang et al. in *Nature Medicine* revealed that glucose metabolism is essential for proliferating keratinocytes, highlighting a potential therapeutic target for pathological hyperproliferation (Zhang et al., 2018). In this review, we propose the conjugation of glucose to antipsoriatic drugs as a novel strategy for targeted delivery through GLUT1 receptors, which may potentially increase the effectiveness, cellular selectivity, and tolerability of antipsoriatic drugs, and thus, revolutionize the management of psoriasis.

Current treatment options and their limitations

The choice of psoriasis treatment depends on a wide variety of factors such as disease severity, its effects on the patient's life, comorbidities, and health care access. Psoriatic patients are often assigned into two groups: those with mild psoriasis and those with moderate to severe psoriasis (Mrowietz et al., 2011). Mild psoriasis affects less than 3% of body surface area (BSA) and responds well to topical application of

vitamin D analogs or corticosteroids, as well as localized UVB phototherapy (O'Neill and Feldman, 2010). Combinations of potent topical corticosteroids and vitamin D analogs or UVB phototherapy are commonly prescribed by dermatologists. With proper adherence, considerable improvement with these therapies may be seen in as little as one week, although several weeks may be required for full benefits (Kleyn et al., 2019). However, treatments including vitamin D analogs, as well as UVB phototherapy, may cause undesirable side effects such as mild irritant dermatitis, hypercalcemia, burning or photoaging (Singh et al., 2016; Kim et al., 2017). On the other hand, moderate to severe psoriasis is defined as involvement of more than 3 to 10 percent of the BSA and usually requires the addition of systemic treatments in combination with topical therapy. The effectiveness of topical therapy alone is limited in cases with severe symptoms, extensive skin lesions and poor quality of life. Additionally, long-term use of topical corticosteroids induces side effects of local skin ulceration or suppression of the hypothalamic-pituitary-adrenal axis (Castela et al., 2012). Notably, methotrexate continues to be used as a first-line systemic agent since 1971, despite the fact that it yields an improvement in only 20 to 30% of all patients with moderate-to-severe psoriasis (Maybury et al., 2014). Toxicity prevents many patients from obtaining favorable outcome from the drug. It has been reported that multiple toxic effects occur in two-thirds of patients, and up to roughly 30% of patients discontinue methotrexate therapy within the first year of treatment because of hepatotoxicity (Bookstaver et al., 2008; Conway et al., 2015). New biological and small-molecule therapies have been developed to complement or replace traditional drugs (Table 1). Biologic molecules which are being currently used for the treatment of psoriasis have been thoroughly described in several reviews (Lowe et al., 2007; Rønholt and Iversen, 2017; Rendon and Schäkel, 2019). Unlike earlier psoriatic treatments, biological agents were designed to target T cells and specific inflammatory mediators such as tumor necrosis factor (TNF) or interleukins (IL). The major concern of biological therapeutics is the impact of long-term chronic immunosuppression, which may potentially lead to increased infection and cancer risk (Lowe et al., 2007). Only conclusions obtained from long-term clinical studies are able to distinguish whether the new therapies are successful. Biologics are also costly, inaccessible for the general public and require repeated injections. Thus, the development of novel drugs to increase effectiveness and reduce toxicity is desirable.

Zhang et al. (2018) have recently found that targeting the glucose transporter GLUT1 and sugar metabolism offers a novel therapeutic strategy for the treatment of psoriasis and other hyperproliferative skin diseases. According to their results, excessively proliferating keratinocytes require glucose uptake through GLUT1, which is not a requisite for healthy skin development and function. The findings indicate that targeting elevated glucose intake and GLUT1 overexpression, which provide clinically corroborated strategies for cancer treatment (Bronstein et al., 2011; Vander Heiden, 2011; Cantor and Sabatini, 2012), could lead to the development of safe and effective therapies for skin diseases (Fig. 1).

Glycoconjugation for selective glucose transporter targeting

Glucose is a fundamental energy source that is absorbed by cells through the plasma membrane. The transporters that allow cellular uptake of glucose can be classified into two distinct families: 1) active and energy-dependent sodium/glucose co-transporters (SGLTs) and 2) passive, facilitative transporters (GLUTs) that use electrochemical gradients to transport glucose. There are 14 mammalian facilitative glucose transporters, among which GLUT1, the most common glucose transporter, is widely overexpressed in many human cancers including hepatic, pancreatic, breast, esophageal, brain, renal, lung, cutaneous, colorectal, endometrial, ovarian, and cervical (Calvo et al., 2010; Szablewski, 2013; Liu and Auguste, 2015). In order to maintain cellular homeostasis, growth, and proliferation, cancer cells significantly increase glucose uptake and the flux of metabolites through glycolysis. This phenomenon, termed “the Warburg effect,” arises from mitochondrial metabolic changes and is a characteristic trait of cancer (Warburg, 1956). Elevated glucose uptake and GLUT overexpression are frequent in neoplasms and provide clinically corroborated strategies for cancer treatment (Bronstein et al., 2011; Vander Heiden, 2011; Cantor and Sabatini, 2012). In general, glycoconjugation offers improved water solubility and stability and the potential for selective targeting. Therefore, it becomes an appealing strategy for targeted delivery of clinically-prescribed drugs (Medina and Owen, 2002; Calvaresi and Hergenrother, 2013; Srinivasarao et al., 2015; Ashley, 2016), with significant advances in the field, reaching as far as late-stage human clinical trials (Pohl et al., 1995; Medina and Owen, 2002; Calvaresi and Hergenrother, 2013; Liu and Auguste, 2015; Granchi et al., 2016; Patra et al., 2016; Srinivasarao and Low, 2017).

Historically, it was suggested that the heightened requirement for glucose, constitutive overexpression of GLUT1, and the persistent metabolism of glucose to lactate is an adaptation to a stressful and dynamic

microenvironment, which is characteristic exclusively for solid tumors, where concentrations of crucial nutrients and oxygen are spatially and temporally heterogeneous (Gatenby and Gillies, 2004; Gatenby et al., 2006). However, recent studies reveal that GLUT1 upregulation is considered to be one of the most immediate events in the pathogenesis of psoriasis by promoting epidermal hyperproliferation, inflammation and angiogenesis (Tao et al., 2008; Tochio et al., 2013; Hodeib et al., 2018). Moreover, it plays a significant role in the evolution of the disease as well as the development of associated comorbidities. It is now well-established that GLUT1 is strongly upregulated in psoriatic lesions, epidermal hyperplasia, and wound healing when compared to healthy skin (Tao et al., 2008; Tochio et al., 2013).

The results of the published data provide a strong rationale for the design and evaluation of glucose-conjugated antipsoriatic drugs to improve their pharmacokinetic and pharmacodynamic properties. Glycoconjugation of antipsoriatic drugs could generate a valuable treatment option for moderate-to-severe forms of psoriasis, as well as comorbidities associated with the disease. In the case of classic comorbidities associated with psoriasis, such as psoriatic arthritis, evidence suggests that the uptake of radiolabeled glucose correlates with the degree of arthritis activity, which may allow the preferential accumulation of glucose-conjugated drugs in the inflamed regions (Mehta et al., 2011; Rose et al., 2014). Moreover, comorbidities related to treatment, such as nephrotoxicity (cyclosporine), hepatotoxicity (methotrexate, leflunomide and acitretin) may be limited due to the expected pharmacokinetic properties of these glucose conjugates.

Perspectives in antipsoriatic drug design

Glycoconjugation generally offers improved water solubility and stability and, if the glycoside of choice is a GLUT substrate, the potential for selective targeting to pathological cells. Glycoconjugation may facilitate the pharmacokinetics of cytotoxic exogenous molecules and ensure their facilitated transport through glucose receptors. Alternatively, compounds that have a sugar moiety may interact with the machinery for the intake and metabolism of glucose. Antimetabolites, which build on sugar structures may, through competitive inhibition, disrupt the cellular metabolism to cause cell death (Harjes et al., 2012; Zhang et al., 2014).

Current evidence has shown that flavonoids, like genistein, suppress psoriasis-related inflammation (Wang et al., 2019). Of the many possible structural modifications of isoflavones, those that form glycoconjugate derivatives deserve special attention. Previous results have shown that sugar derivatives of genistein were not only able to significantly facilitate the transport of polyphenol into the intracellular compartment, but also to modify its mechanism of action and exert a dozen times higher therapeutic effect than genistein alone (Rusin et al., 2011; Gogler-Piglowska et al., 2012). These results provide a strong rationale to further develop and explore the biological effect of glycoconjugates of active substances used in clinical practice. Thus, we propose methods for the synthesis of conjugates of clinically used antipsoriatic drugs, namely cyclosporine, acitretin, and tofacitinib with glucose. It is expected that at least some of the undesirable effects of these drugs can be diminished by chemical modification due to preferential influx into the target cells. Moreover, it is assumed that the derivatives may exhibit increased cellular selectivity and more significant therapeutic effect. The design of specific targeting ligands has been presented in several excellent review publications (Calvaresi and Hergenrother, 2013; Granchi et al., 2016), and our experience in the synthesis of glycoconjugates of biologically active compounds (Pastuch-Gawolek et al., 2016) is the starting point for planning complex glucose derivatives of selected drugs used in psoriasis therapy.

Glycoconjugate of acitretin

Acitretin is a second-generation synthetic retinoid administered for moderate to severe psoriasis (Boehncke and Schön, 2015). Although acitretin is a widely-used systemic agent for the treatment of psoriasis, the efficacy of the drug is notoriously variable. As reported, there was a dose-response trend, with the highest doses of acitretin (50–75 mg/day) proving more effective than lower doses (10–25 mg/day) (Goldfarb et al., 1988). Hyperlipidemia is an obvious side effect of acitretin, particularly hypertriglyceridemia (Orfanos et al., 1997). Further side effects include arthralgia, mucocutaneous dryness, and photosensitivity. These factors limit acitretin's clinical use, especially in patients with other risk factors for cardiovascular disease.

Retinoic acid analogs have emerged as important therapeutic agents for the treatment of various skin diseases (e.g., acne and psoriasis) and as potential cancer chemopreventive agents. Therefore, synthesis of acitretin derivatives with increased solubility as well as stability toward hydrolysis and oxidation was

critical. Balakrishnan et al. reported that glucuronide conjugates of retinoids were active and exhibited improved hydrolytic stability (Balakrishnan et al., 1997). However, it was found that retinoid glucuronides do not bind to retinoid receptors, and their potential application in psoriasis was not reported. We propose the synthesis of D-glucose conjugates, potential ligands of GLUT1, that will undergo intracellular hydrolysis into acitretin and glucose. The strategy for the synthesis of the conjugate is shown in Figure 2A. Amide formation is among the most widely studied and used transformation in synthetic chemistry. A vast range of coupling agents and carboxyl activating species, therefore, exist for undertaking such reactions (Valeur and Bradley, 2009; Koniev and Wagner, 2015). The known 2-aminoethyl- or 3-aminopropyl- β -D-glucoside was treated with acitretinamide in the presence of carbon diimides as a coupling agent (e.g. *N*-(3-(dimethylamino)propyl)-*N'*-ethylcarbodiimide (EDC), dicyclohexylcarbodiimide (DCC) (Valeur and Bradley, 2009; Koniev and Wagner, 2015). The reaction is routinely conducted according to proposed procedures. Deprotection of the conjugate sugar portion is performed under standard conditions (basic conditions) by treatment with sodium methanolate. Moreover, taking into account the higher stability of *S*-glycosides in comparison with *O*-glycosides, the synthesis of acitretin glycoconjugates derivatives of 1-thioglycosides, containing an amino group in their aglycon, is shown in Figure 2A (and follows a similar route as in case of *O*-glycoside).

Glycoconjugate of cyclosporin

Cyclosporin is a widely-used immunosuppressant. Despite its everyday clinical use, it is associated with several side effects that include high blood pressure, headache, nephrotoxicity, increased hair growth, and vomiting, as well as increased risk of infection, lymphoma, and liver problems (Tedesco and Haragsim, 2012). The increased blood pressure can cause cardiovascular events; it is thus recommended that the lowest effective dose for people requiring long-term treatment be used (Robert et al., 2009). Cyclosporin exhibits very poor solubility in water, and, as a consequence, suspension and emulsion forms of the medication have been developed for oral administration and injection. We expect that glycoconjugates may increase the bioavailability of the drug and optimize the formulation. The attachment of the sugar to result in a cyclosporine derivative glycopeptide is possible due to the functionalization of a double C=C bond. The attractiveness of designed compounds stems from the belief that *C*-glycosides are better potential drug candidates because, compared to their *O*-glycoside parents, they are not only more stable

to acid, but also to glycosidases and thus will have better biological half-lives. We describe here a route to a C-glycoside analog of cyclosporin. Given its robustness and general ease of implementation, transition metal-catalyzed olefin metathesis has become an increasingly ubiquitous method for generating C–C double bonds in a wide variety of fields including organic synthesis, green chemistry, and biochemistry (Grubbs and Khosravi, 2015). In the method reported here, the critical step is an olefin cross-metathesis of allyl derivatives of D-glucose and peptide. Planned substrates are methyl 6-*O*-allyl-D-glucoside, and allyl-D-glucopyranoside prepared according to known and effective procedures. The critical issue is to preserve the *E*-configuration of substituents on the cyclosporin derivatives. Recently, ruthenium-based olefin metathesis catalysts bearing dithiolate ligands have been employed to generate olefins with high selectivity, which made it possible to obtain almost exclusively the *E* isomer (>99% *E*) (Ahmed and Grubbs, 2017). These catalysts demonstrate significantly improved initiation, resulting in considerably increased activity of these catalysts in reactions of *trans* olefins and demonstrating higher yields at shorter reaction times while maintaining high stereoselectivity of products (>99% *E*). The synthesis project is shown in Figure 2C. In the planned reaction of olefin cross-metathesis leading to cyclosporine glycoconjugates, it was decided to use 6-*O*-allyl-D-glucoside, allyl- β -D-glucopyranoside, 1C-allyl- β -D-glucopyranoside as the sugar substrates.

Glycoconjugate of tofacitinib

Janus activated kinases (JAKs) are a family of receptor-associated tyrosine kinases involved in several physiological functions such as immune responses and are related to autoimmune and inflammatory diseases (Babon et al., 2014; Schwartz et al., 2016). Tofacitinib is a JAK inhibitor approved for the treatment of active psoriasis, as well as rheumatoid arthritis.

A comprehensive analysis of the different synthetic methods used to prepare this active pharmaceutical ingredient was reported (Carvalho et al., 2019). The synthons (the building blocks) used in the synthesis of tofacitinib are 4-methyl 3-*N*-methyl-*cis*-piperidine and 2,4-dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine. The nucleophilic substitution of chlorine at the C-4 pyrimidine of the derivative with the amine group from the piperidine derivative according to a S_NAr mechanism is performed in the presence of a base such as K₂CO₃ or Na₂CO₃ (Renom-Carrasco et al., 2016).

In our proposal (Figure 2B) the compound obtained in this reaction was a substrate for a second nucleophilic substitution reaction with a sugar derivative. Displacement of a chlorine atom in this compound by treatment with per-*O*-acetylated D-glucose derivatives leads to the formation of the glycoconjugate. After removing the protecting benzyl group from the piperidine nitrogen atom by simple hydrogenolysis, this atom can be further functionalized. Price et al. described a single-step process for direct amidation of alkyl cyanoacetates using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in nBuOH (Price et al., 2009). Under the proposed conditions, deacetylation of the sugar unit also takes place, and as a result, the desired drug is obtained.

Assessment of chemical properties, the bioactivity and the biodistribution of glycoconjugates

After synthesis and traditional LC separation, the compound must be characterized in order to confirm the desired structure. It is advisable to perform the validation with both chromatographic and spectroscopic methods (¹H NMR, ¹³C NMR, HRMS), as well as to determine the optical purity using polarimetry. Compound stability, solubility, cellular uptake, biodistribution, and bioactivity need to be comprehensively evaluated to determine the potential clinical application of the conjugate. There are several well-established methods to evaluate the cellular uptake of glycoconjugates. Barnett et al. (Barnett et al., 1973) reported that GLUT-mediated drug entry could be measured using radiolabeled glucose, whereas Kim et al. (Kim et al., 2012) suggest the use of 2-NBDG, a fluorescent analog of glucose, as a marker for visualization of cellular uptake and biodistribution of a fluorescent deoxyglucose derivative. For confirmation as to whether glucose transporters are involved in the uptake of the glucose-conjugated compound, cytochalasin B and phloretin can be used as known inhibitors of GLUTs (Tomaszowski et al., 2017). After evaluation of the optimal dosage of glucose conjugates *in vitro*, it is advisable to perform *in vivo* studies on psoriasis mouse models to determine the pharmacokinetics and pharmacodynamics, and in particular, the maximum tolerated dose, as well as anti-inflammatory properties. Although there is a scarcity of data regarding the administration of glucose derivatives in psoriatic animal models, protocols for the evaluation of glucose conjugates in cancer therapy could be used as a reference (Liu et al., 2017). Moreover, drug serum stability, biodistribution in collected blood and urine, and visualization of the localization in the whole animal can be assessed using radiolabeled glucose (Stüben et al., 1996) or real-time whole-body NIR optical imaging (Zhou et al., 2009).

Conclusions

Notable advances in our understanding of psoriasis, courtesy of basic science observations, has opened new avenues for the treatment of skin diseases. Recent findings concerning the fundamental role of glucose metabolism and GLUT1 expression in the pathogenesis of psoriatic lesions brought to light approaches that have garnered much attention and proved successful in cancer treatment. Substantial advances in the emerging field of glycoconjugation highlight the rationale for the development of glucose-conjugated antipsoriatic drugs to increase their effectiveness, cellular selectivity, and tolerability. The presented approach that exploits the heightened glucose requirement of keratinocytes may revolutionize the management of psoriasis.

Authorship Contributions:

Wrote or contributed to the writing of the manuscript: Agrawal and Makuch (conception); Woźniak and Pastuch-Gawolek (methodology); Makuch and Krawczyk (original draft preparation and writing); Szeja (formal analysis and supervision).

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Footnotes

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Figure Legends

Figure 1. Transport of glucose conjugated antipsoriatic drugs through GLUT1 in keratinocytes.

In contradistinction to healthy keratinocytes, hyperproliferative keratinocytes comprise of overexpressed GLUT1 transporters, which contribute to significantly higher uptake of glucose conjugated drugs. As a result, in chronic inflammation, the glucose conjugated antipsoriatic drugs may lead to reduced inflammation and hyperproliferation of keratinocytes. The intracellular cleavage of acid-labile linkers in the more acidic environment results in controlled drug release in hyperproliferative keratinocytes.

Figure 2. Synthesis of glucose conjugated antipsoriatic drugs. Synthesis of A) acitretin glycoconjugate, B) tofacitinib glycoconjugate and C) cyclosporin glycoconjugate.

Tables

Table 1. FDA approved traditional and biological therapies for psoriasis. Agents have been classified into two main groups: 1) systemic immunosuppressives used for the treatment of moderate to severe psoriasis; 2) biological agents divided into TNF- α inhibitors, interleukin 17 inhibitors, as well as interleukin 23 and related cytokine inhibitors.

Class	Compound	Mechanism of action
Traditional agents commonly used in treatment of moderate to severe psoriasis	Methotrexate	A folate antimetabolite that inhibits T-cell activation as well as DNA synthesis and repair (Chan and Cronstein, 2013)
	Cyclosporine	A calcineurin inhibitor that leads to reduced production of interleukin-2 (Matsuda and Koyasu, 2000)

	<p>Apremilast</p>	<p>A phosphodiesterase 4 (PDE4) inhibitor that leads to increased intracellular cAMP levels to regulate various inflammatory mediators (e.g, decreases levels of TNF-α and interleukin-23, increases level of interleukin-10) (Schafer, 2012)</p>
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		Tofacitinib	An inhibitor of interleukin-2-induced phosphorylation of JAK3 and STAT5, which are involved in immune cell function (Hodge <i>et al.</i> , 2016)
		Fumaric acid esters	Fumarate derivatives that activate Nrf2 to inhibit the production of pro-inflammatory cytokines such as IL-12 and IL-23 (Balak, 2014)
		Acitretin	A retinoid that binds to and activates retinoid receptors to normalize keratinocyte differentiation in the epidermis (Tippmann <i>et al.</i> , 2009)
Biological agents	TNF-alpha inhibitors	Etanercept	A recombinant protein that binds to the Fc portion of IgG and blocks soluble TNF- α interaction with receptors on the cell surface (Goffe and Cather, 2003)

		Infliximab	A chimeric monoclonal antibody that interferes with endogenous TNF- α (Guo <i>et al.</i> , 2013)
		Adalimumab	A recombinant monoclonal antibody against TNF- α (Mease, 2007)
		Certolizumab pegol	A pegylated Fab' fragment of humanized monoclonal antibody against TNF- α ; selectively binds and neutralizes the activity of human TNF- α (Acosta-Felquer <i>et al.</i> , 2016)
	Interleukin 17 inhibitors	Secukinumab	A human IgG1 κ monoclonal antibody that selectively binds to interleukin-17A and inhibits the interaction of this cytokine with the IL-17 receptor (Fala, 2016)
		Ixekizumab	A humanized IgG4 κ monoclonal antibody against IL-17A, that inhibits the release of proinflammatory cytokines and

			chemokines (Monin and Gaffen, 2018)
		Brodalumab	A human monoclonal IgG2 antibody that acts as an antagonist of IL-17 receptor A (IL-17RA) to block the release of proinflammatory cytokines and chemokines (Monin and Gaffen, 2018)
	Interleukin 23 and related cytokines inhibitors	Ustekinumab	A human IgG κ monoclonal antibody that binds with high affinity to p40 subunit of both (IL)-12 and IL-23 to reduce the expression of key cytokines such as MCP-1, TNF- α , IP-10, and IL-8 (Benson <i>et al.</i> , 2011)
		Guselkumab	A human IgG1 λ monoclonal antibody that selectively blocks the IL-23 receptor and reduces the serum levels of IL-17A, IL-17F,

			and IL-22 (Al-Salama and Scott, 2018)
		Tildrakizumab	A human IgG1 κ monoclonal that binds to the p19 subunit of interleukin (IL)-23, and consequently inhibits its interaction with the IL-23 receptor (Papp <i>et al.</i> , 2015)
		Risankizumab	A human IgG1 monoclonal antibody against the p19 subunit of interleukin (IL)-23, resulting in inhibition of its interaction with the IL-23 receptor (Haugh <i>et al.</i> , 2018)



