


REVIEW ARTICLE

Anticancer treatments and photosensitivity

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Abstract

Drug-induced photosensitivity is associated with a wide range of anticancer treatments, including conventional chemotherapeutic agents, targeted anticancer therapies, and immune checkpoint inhibitors. These dermatologic adverse events can have a major impact on the well-being and quality of life of cancer patients, leading to dose modifications and interruption or discontinuation of anticancer treatments in severe cases. However, the heterogeneous nature of the photosensitive reactions induced by these agents, as well as the common concomitant use of other potentially photosensitizing drugs (antibiotics, voriconazole, nonsteroidal anti-inflammatory drugs, etc.), can make the diagnosis and, therefore the prevention, of these adverse events particularly challenging. The aim of this review is to describe the most characteristic forms of photosensitivity observed in patients being treated with anticancer treatments, including phototoxicity and photoallergy, and other potentially photo-induced manifestations such as UV recall, exaggerated sunburn reactions associated with treatment-related vitiligo, drug-induced cutaneous lupus erythematosus, and UV-induced hyperpigmentation. We also discuss the photosensitive reactions recently reported with new-generation targeted anticancer therapies and immune checkpoint inhibitors and highlight the importance of continued surveillance to identify photosensitizing agents, and of educating patients on the need for preventive UVA/UVB photoprotective measures.

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Conflicts of interest

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Introduction

Skin photosensitivity refers to a range of dermatologic conditions that are caused or exacerbated by sunlight exposure.^{1,2} Photosensitive dermatitis can be caused by endogenous or exogenous factors, with drugs being amongst the most common exogenous photosensitizing agents.^{1,2} Drug-induced photosensitivity can occur when components of topical or systemic agents present in the skin act as exogenous chromophores and are activated by a component of the electromagnetic spectrum of sunlight, most commonly ultraviolet A (UVA) radiation (320–400 nm).^{1,3,4}

Photosensitivity: Phototoxicity and photoallergy

Drug-induced photosensitivity can be classified as either phototoxic or photoallergic reactions based on the underlying pathophysiological mechanism, although differences in the time to

onset, clinical presentation, and incidence of these reactions have also been reported (Table 1).^{1,3,4}

Phototoxic drug reactions are the most frequent type of drug-induced photosensitivity and can occur in any patient following exposure to a photosensitizing agent and UV radiation. Phototoxicity corresponds to a dose-dependent reaction, with respect to both the causative agent and sunlight exposure, and results from a direct inflammatory, nonimmune-mediated, response to cytotoxic damage caused by UV-induced generation of reactive oxygen species.^{4,5} Clinically, phototoxic reactions typically manifest as an exaggerated sunburn response with clearly demarcated erythema and oedema occurring on sun-exposed skin. A relative sparing of the deep furrows on the face and interdigital folds on the dorsal surface of the hands can also be observed. Onset is usually rapid, occurring within hours of exposure to the agent and UV radiation. The progressive development of a localized or

Table 1 Main characteristics and systemic agents associated with drug-induced phototoxicity and photoallergy

		Phototoxicity	Photoallergy
Incidence		High	Low
Clinical characteristics		Erythematous lesions	Ecematous lesions
Localization		Sun-exposed skin	Sun-exposed skin with spread to unexposed areas
Onset		Immediate – <24 h after exposure	>24 h –
Pigmentary changes		Frequent	Rare
Histopathology		Necrotic keratinocytes, dyskeratosis, dermal oedema, and vasodilation; lymphocytic and neutrophilic infiltration of the dermis	Epidermal spongiosis, vesiculation, exocytosis of lymphocyte exocytosis, and a perivascular inflammatory infiltrate
Pathophysiology		Inflammatory, nonimmune-mediated cytotoxic damage	Immune-mediated: T cell-mediated type IV hypersensitivity
Dose dependent		Yes	No
Sensitization		Yes	No
Common causative agents*			
Anti-infectious	Fluorquinolones	Lomefloxacin,	Lomefloxacin, Enoxacin
	Tetracyclines	Tetracycline, Doxycycline, Demeclocycline	
	Antimycotics	Griseofulvin, Voriconazole	
	Antimalarials	Quinine	Quinine
Anti-inflammatory	NSAIDs	Naproxen, Ketoprofen, Tiaprofenic acid	Ketoprofen, Tiaprofenic acid, Piroxicam
Anticancer	Antimetabolites	Methotrexate ²	
	Small molecule inhibitors	Vemurafenib, Vandetanib, Dabrafenib	
Cardiovascular	Diuretics	Hydrochlorothiazide, Furosemide	Hydrochlorothiazide
	Antiarrhythmics	Amiodarone	Amiodarone
Nervous system	Antidepressants	Hypericum	
	Antipsychotics	Promethazine	Promethazine
	Others	Cevimeline	
Metabolism/endocrinologic	Fibrates		Fenofibrate
Others	Psoralens	8-Methoxypsoralen	
	Porphyrins	Porfimer sodium	
	Antifibrotic	Pirfenidone	

*Common causative agents were identified as drugs with a high level of evidence of their photosensitizing effects (i.e. number of publications $n \geq 15$) according to Hofmann and Weber (2021),⁴ and classed as causing phototoxicity and/or photoallergy according to Gould *et al.* (1995),¹ and Monteiro *et al.* (2016).⁵⁰

more diffuse hyperpigmentation is common once the acute reaction has resolved.^{1,3,4}

In contrast, photoallergic drug reactions are mediated by a T cell-mediated immune mechanism, resulting in a delayed type IV hypersensitivity response. Photoallergy therefore only manifests in pre-sensitized individuals and is reported much less frequently than phototoxic drug reactions.^{3,4} The most common clinical presentation is an eczematous eruption that appears mainly on sun-exposed skin. However, photoallergic dermatitis often lacks the clear demarcation observed with phototoxicity and may develop into a more diffuse eruption with repeated exposure.¹ Onset generally occurs 24–72 h after sunlight exposure and treatment with causative agent but, as is common with other delayed-type hypersensitivity reactions, symptoms tend to worsen and peak 48–72 h after onset. Although most cases resolve after removal of the causative agent and sun avoidance, persistent photoallergic light reactions have been reported.^{1,4}

Anticancer treatments and photosensitivity

Photosensitivity has been reported in association with a wide range of drugs and/or drug compounds (Table 1). Although photosensitivity may seem rare in oncology, anticancer treatments have been identified as one of the top five classes of drugs associated with photosensitivity, making up around 12% of reported photosensitizers.⁴ Conventional chemotherapeutic agents,⁶ targeted anticancer therapies,^{5,7} and immune checkpoint inhibitors⁷ have all been reported to induce photosensitive dermatitis.

In this review, we describe the most characteristic photosensitivity reactions observed in cancer patients being treated with anticancer treatments, including phototoxicity and photoallergy, as well as other manifestations potentially related to photo-exposure, including UV recall, vitiligo-like reactions, drug-induced cutaneous lupus erythematosus (CLE), and UV-induced hyperpigmentation.^{5–10} Details of the literature search and selection process are provided as [Supplementary Material](#).

Chemotherapeutic agents

Phototoxic skin reactions

Fluorouracil (5-FU) and fluorouracil-related compounds (tegafur and capecitabine), together with vinblastine, dacarbazine, and methotrexate, are among the conventional chemotherapeutic agents that have been most widely reported to cause phototoxic reactions. Simultaneous exposure to these agents and UV radiation can result in the typical phototoxic exaggerated sunburn response, characterized by erythema and oedema, and often accompanied by pain, tenderness, and pruritus. Blistering and desquamation may also occur in severe cases.^{1,8} Sun-exposed areas on the face, chest, arms, and legs, as well as the dorsa of the hands and posterior region of the neck are the sites most frequently involved. Hyperpigmentation is also common after the acute reaction has resolved, and may persist for several months⁸ (see Section [Diffuse or localized hyperpigmentation](#)).

While the typical exaggerated sunburn response is the most common reaction observed with 5-FU, photodistributed lichenoid dermatitis has been reported in some patients being treated with tegafur⁹ and capecitabine^{3,11,12} (Fig. 1a). In addition, methotrexate has been reported to cause phototoxic reactions. However, methotrexate-induced photosensitivity may also manifest as a UV recall reaction (see Section [UV recall](#)). It is

important to note that true phototoxicity induced by chemotherapy remains rare and that cancer patients are also frequently treated in combination with other drugs such as anti-infectious agents (e.g. doxycycline or voriconazole), antihypertensive drugs (e.g. hydrochlorothiazide), or nonsteroidal anti-inflammatory drugs (NSAIDs), which are commonly associated with phototoxic reactions¹³ (Fig. 1b). All drugs being taken by the patient should therefore be screened for their potential to induce phototoxic reactions. For example, it may be difficult to identify the causative drug in patients who develop phototoxicity reactions when being treated for advanced colorectal cancer with a combination of 5-FU and the epidermal growth factor receptor (EGFR) inhibitor panitumumab, and who are being treated concomitantly with doxycycline to limit the risk of developing an acne-like rash induced by anti-EGFR.

Diffuse or localized hyperpigmentation

Hyperpigmentation is a common cutaneous reaction reported in patients receiving chemotherapy, with capecitabine, 5-FU, cisplatin, busulfan, doxorubicin, bleomycin, pemetrexed, and cyclophosphamide being amongst the most frequently identified causative agents.⁶ The reaction is most often caused by the direct toxicity of these chemotherapeutic agents to melanocytes, associated with secondary stimulation of melanogenesis.⁶ The clinical



Figure 1 Photosensitivity and chemotherapy: (a) photodistributed lichenoid dermatitis with the chemotherapeutic agent capecitabine; (b) a phototoxic reaction in a patient treated concomitantly with chemotherapy and voriconazole; (c) progressive development of hyperpigmentation with cyclophosphamide (dorsal surfaces of the hands); (d) UV recall with docetaxel; and (e) diffuse annular lesions of subacute lupus erythematosus induced by pemetrexed.

presentation and distribution of the pigmentary changes (diffuse or localized) has been found to vary considerably, even between patients undergoing similar treatments.⁶ Indeed, chemotherapy has been reported to induce a wide range of pigmentary changes involving the skin, nails, and mucous membranes, e.g. eruptive nevi, serpentine supravenuous hyperpigmentation, flagellate or reticulate hyperpigmentation, melanonychia, and post-inflammatory hyperpigmentation (associated with repeated trauma, toxic erythema of chemotherapy, etc.).^{6,10,14}

Although post-inflammatory hyperpigmentation following a phototoxic reaction induced by chemotherapeutic agents such as 5-FU, tegafur, vinblastine, dacarbazine, and doxorubicin can occur in some cases,⁶ localized or more diffuse hyperpigmentation after UVA/UVB exposure can also develop progressively without an initial inflammatory phase. These lesions are most prevalent in areas regularly exposed to UVA and UVB light, notably the dorsal aspect of the hands (Fig. 1c) and the face. The clinical presentation may be that of a progressive tan, particularly in patients treated with capecitabine for a long period of time. Other types of induced mucocutaneous hyperpigmentation are often associated, for example eruptive nevi occurring predominantly in the palmoplantar areas. Progressive development of a diffuse brown/bronze hyperpigmentation, even in non-sun-exposed areas like palmar creases, has been also described with busulfan (busulfan tan).^{8,10,15}

Although the hyperpigmentation usually fades after completion of chemotherapy, resolution of the pigmentary alterations is a gradual process that can take months or years. These adverse events (AEs) are therefore a major concern for patients and need to be addressed through preventive photoprotective measures in individuals initiating therapy with potential photosensitizing agents¹⁰ (see Section [Management recommendations and initiatives](#)).

UV recall

UV recall is an exceptional inflammatory phototoxic reaction that occurs after administration of a systemic therapy and strictly affects areas of skin that have been involved in a prior episode of UV-induced solar erythema.^{16,17} Other sources of irradiation have also rarely been reported to be involved in recall reactions, including lasers (laser recall).¹⁸

The reaction was initially described in patients being treated with methotrexate, but UV recall has also been reported after the administration of gemcitabine, taxanes (Fig. 1d), and etoposide, as well as even more rarely in patients taking antibiotics and other drugs.^{17,19,20} The reported intervals between the initiation of chemotherapy and the prior episode of UV-induced solar erythema vary widely: although in most cases the interval is short (a few days or weeks), UV recall has been also reported in patients initiating chemotherapy months or even a year after an episode of UV-induced solar erythema.¹⁶ The skin reaction may occur a few hours or days after the initial infusion of the causative agent, and typically manifests as a pruritic erythematous rash

associated with pain, blisters, and burning in severe cases. Histopathology is nonspecific, often revealing the presence of varying degrees of perivascular inflammatory cell infiltrates and apoptosis.¹⁶ UV recall does not usually lead to discontinuation of treatment as the reaction is often absent or less severe during subsequent treatment cycles.¹⁷ Topical and systemic corticosteroids can be useful for relieving patient symptoms.

Targeted anticancer therapies

Photosensitive dermatitis is not limited to conventional chemotherapy and can also occur in patients treated with a range of targeted anticancer therapies. Vemurafenib and vandetanib are the two targeted anticancer therapies for which phototoxicity has been noted as a common dermatologic AE.^{7,21,22} It should also be noted that photosensitivity reactions have also been recently reported with newly-developed targeted anticancer therapies.^{23–26} Finally, the majority of the targeted anticancer therapies inhibiting c-KIT may induce progressive depigmentation of the skin and/or hair, which may lead to exacerbated sensitivity after UV-exposure in treated patients.^{27–29}

Selective BRAF inhibitor vemurafenib

Vemurafenib, a first-in-class BRAF inhibitor, is used either alone or in combination with the mitogen-activated protein kinase (MEK) inhibitor cobimetinib for the treatment of patients with advanced BRAF V600-mutant melanoma.³⁰ Phototoxicity is one of the most frequent dermatologic AEs occurring in vemurafenib-treated patients, being reported in 35%–63% of patients²¹ with a relative risk of 2.14 (95% CI: 0.52–8.91).⁷ In the majority of cases, the reaction was classed as mild to moderate (Fig. 2a–c); however, in around 10% of cases, the patients experienced grade 3 phototoxicity (painful blistering) that necessitated treatment interruption.³¹ UVA has been clearly identified as the type of radiation associated with vemurafenib-induced phototoxicity,³² and all patients receiving vemurafenib treatment should be educated prior to therapy initiation on the need for UVA-UVB photoprotection (see Section [Management recommendations and initiatives](#)).

RET inhibitor vandetanib

The multikinase inhibitor (MKI) vandetanib targets the EGFR, vascular endothelial growth factor (VEGF) receptors 1, 2, and 3, and the rearranged during transfection (RET) receptor.³³ It is indicated for use in the management of advanced medullary thyroid carcinoma. Photosensitivity is a frequent dermatologic toxicity during vandetanib treatment (Fig. 2d,e), affecting roughly just over one-third of subjects.²² Moderate-to-severe exaggerated sunburn reactions are the most common form of photosensitivity reported, leading to treatment interruption in some cases. Other rarely reported manifestations include photodistributed lichenoid eruptions, photo-induced erythema multiforme, and subacute CLE (SCLE; see Section [Drug-induced cutaneous lupus](#)



Figure 2 Photosensitivity and targeted anticancer therapies: (a–c) grade 2 phototoxic reactions with the selective BRAF inhibitor vemurafenib, exclusively involving skin in photo-exposed areas; (d) blue dots with hyperpigmentation associated with vandetanib therapy; (e) type 1 photo-onycholysis with vandetanib therapy; and (f) exaggerated sunburn occurring on pre-existing vitiligo-like lesions induced by pazopanib.

erythematosus).^{22,34,35} In addition, vandetanib treatment has been associated with nail involvement, with the development of painful medial photo-onycholysis³⁴ (Fig. 2e). This nail toxicity is probably underestimated in daily practice.

Hyperpigmentation is also a common AE of vandetanib therapy, developing in around 20% of treated patients and often occurring following or concomitantly with the skin eruptions.^{22,34} The most characteristic vandetanib-induced pigmentary change is the occurrence of blue-grey spots appearing on sun-exposed areas³⁶ (Fig. 2d); however, more diffuse or dusky photodistributed patterns of blue-grey or brown hyperpigmentation have also been reported. Reports of photosensitization occurring through glass, phototesting of affected patients, and the results of *in vitro* studies all indicate that vandetanib-related photosensitivity is mediated by a UVA-induced phototoxic mechanism, associated with the accumulation of melanophages in the dermis and melanin incontinence.^{22,34,35}

Newer-generation targeted anticancer therapies and photosensitivity

Evidence is already accumulating to suggest that several of the more recently developed targeted anticancer therapies have the potential to also induce photosensitive reactions.

- Photoallergic reactions after UVB exposure have been reported in patients receiving therapy with mogamulizumab, an anti-CC chemokine receptor 4 (CCR4) monoclonal antibody approved for the treatment of several types of T-cell lymphoma, including mycosis fungoides/Sezary syndrome.²³ However, this remains to be confirmed.³⁷
- The newer-generation anaplastic lymphoma kinase (ALK) inhibitor, brigatinib, which is used in the treatment of advanced ALK-rearranged non-small cell lung cancer, has been also associated with phototoxic reactions.²⁴
- Photosensitivity was also reported as a treatment-emergent AE in more than 15% of women treated with rucaparib, a small molecule poly(ADP-ribose) polymerase (PARP) inhibitor, as a maintenance therapy for recurrent platinum-sensitive ovarian carcinoma.²⁵
- Finally, ulixertinib, a first-in-class ERK (extracellular signal-regulated kinase) 1/2 inhibitor with clinical activity in BRAF- and NRAS-mutant cancers, has been associated with the development of skin toxicities in more than 75% of cases. In particular, photosensitive reactions may occur in 3%–9% of patients.²⁶

These reports highlight the need for ongoing surveillance of the cutaneous AEs associated with newly-developed targeted anticancer therapies.

Depigmentation and photosensitivity with targeted anticancer therapies

A systematic review estimated that the overall incidence of all-grade skin pigmentary changes in patients treated with targeted anticancer therapies was 17.7% (95% CI: 11.9–25.4).²⁷ Pigmentary changes involving skin hypopigmentation were most commonly associated with the use of MKIs resulting in blockade of the c-KIT pathway, including cabozantinib, sunitinib, pazopanib, and imatinib.²⁷ C-KIT is a known regulator of melanogenesis, and patients treated with MKIs targeting the KIT protein have been reported to develop dose-dependent, patchy or diffuse, hypopigmentation of the skin, leading to an increased risk of exaggerated sensitivity to sun exposure as well as sunburn on sun-exposed areas (Fig. 2f). A progressive hair depigmentation, with involvement of the scalp, the eyelashes, and eyebrows, is usually associated.^{28,29}

Drug-induced cutaneous lupus erythematosus

Drug-induced CLE is another form of dermatological toxicity associated with cancer treatments. It has been widely reported in patients receiving conventional chemotherapeutic agents, including taxanes, antimetabolites (capecitabine, 5-FU, and gemcitabine), pemetrexed (Fig. 1e), and hydroxyurea.^{10,38,39} In a recent retrospective study of 88 patients diagnosed with CLE, chemotherapeutic agents were identified as a causative or aggravating factor in around 10% of cases.⁴⁰

Subacute CLE is the most common drug-induced CLE subtype, characterized by localized or widespread nonscarring, annular, or papulosquamous eruptions.³⁸ It should be noted that these lesions occur mainly, but not exclusively, in non-photo-exposed areas. Drug-induced SCLE is indistinguishable from idiopathic SCLE, with the vast majority of cases testing positive for anti-SSA autoantibodies.³⁸ In addition to SCLE, 5-FU and fluorouracil-related agents have also been reported to cause chronic CLE. In the cases reported so far, the chronic lesions typically appeared on sun-exposed areas, such as the scalp and/or face, and were not associated with the production of anti-SSA autoantibodies.^{40,41}

In contrast, the development of drug-induced CLE is very rare with targeted anticancer therapies. However, it should be noted that a higher incidence of SCLE or chronic CLE has been reported in patients treated with the cyclin-dependent kinase (CDK) 4/6 inhibitor, palbociclib.^{42,43} Finally, anti-programmed cell death-1 (anti-PD-1) monoclonal antibodies are also able to induce or exacerbate CLE.^{44,45}

Although most cases of drug-induced CLE tend to resolve within weeks after withdrawal of the causative agent, symptomatic management of the skin lesions is usually warranted in cancer patients due to the potentially life-saving nature of their cancer treatment. The use of topical steroids, oral prednisone, hydroxychloroquine, and topical tacrolimus, either alone or in combination,³⁸ allows continuation of anticancer therapy in most cases.

Photosensitivity and immune checkpoint inhibitors

Dermatologic toxicities appear to be amongst the most common immune-related AEs associated with immune checkpoint inhibitors (ICIs).⁴⁶ Overall, the anti-PD-1 nivolumab has been associated with an all-grade incidence of photosensitivity estimated at 1.5% (95% CI: 0.5%–4.4%).^{7,47}

Moreover, a progressive vitiligo-like skin hypopigmentation may occur. These pigmentary changes have been reported in almost all cases in patients treated for melanoma with anti-PD-1 agents, with an overall incidence of 7%–8%. Vitiligo-like lesions occur less commonly in patients treated with anti-cytotoxic T-lymphocyte-associated protein-4 (anti-CTLA-4) agents.^{46,48} Lesions mainly develop in sun-exposed areas and thus increase the risk of exaggerated sunburn reactions.

Diagnostic challenges and management of photosensitivity

Diagnostic challenges

Given the range of clinical manifestations associated with the photosensitive reactions induced by anticancer agents, establishing a diagnosis can be challenging and requires close evaluation of the clinical presentation and medication history of the patient. Phototesting to determine the minimal erythema dose (MED) in response to UVA or UVB radiation before and after discontinuation/interruption of treatment, photopatch testing to screen for photoallergic reactions, rechallenge tests, and histopathology may also be needed to exclude other diseases and confirm the diagnosis in cases where anticancer treatments have not previously been identified as photosensitizing agents.^{1,3} However, some forms of photosensitivity can be difficult to identify and time-consuming to diagnose, particularly in the context of oncology patients. Indeed, the clinical situation of cancer patients often does not allow for a progressive and standardized approach to confirm the diagnosis. Furthermore, these patients are often treated in combination with a range of other therapies that may be potentially involved in the occurrence of photosensitive dermatitis, and it can be very challenging to identify the likely causative agent. Therefore, therapeutic management, which may include treatment discontinuation depending on the severity of the reactions, remains mostly empirical.

Management recommendations and initiatives

Photosensitivity reactions, like all dermatologic AEs associated with anticancer treatments, can have a profound effect on patient well-being and quality of life, leading to dose modifications and treatment interruption or discontinuation in severe cases.⁴⁹ Patient education and prevention are the cornerstones of management of photosensitivity. Patients should be advised to avoid prolonged UVA and UVB exposure and encouraged to

take protective measures such as systematically applying broad-spectrum sunscreens and wearing UV-protective clothing, hats, and sunglasses.^{1,3,21,27} Patients should also be made aware that UVA can penetrate glass,³² and be reminded to protect the nails in some specific cases. In cases where preventative measures fail and photosensitivity occurs, symptomatic treatment with topical or systemic corticosteroids may help to reduce the impact of the photosensitive eruptions on patient quality of life and allow potentially life-saving cancer therapies to be continued without dose modification.^{1,3}

Raising awareness of the clinical characteristics of photosensitivity to facilitate the identification of photosensitizing agents, and improving the knowledge of clinicians, particularly oncologists, concerning the risk of developing photosensitive reactions are key factors for the prevention and better management of photosensitivity in cancer patients. Several initiatives have already been established to facilitate the recognition of dermatologic toxicities associated with cancer therapy. One such initiative was the development of the *Side Onco Skin* mobile app (available from the App Store and Google Play), which provides information on the main dermatologic toxicities associated with anticancer treatments and can also be used to search for the main dermatologic toxicities induced by anticancer treatments.

Conclusions

Drug-induced photosensitivity is known to be associated with a wide range of anticancer treatments, and new patterns of photosensitivity appear likely to be established as new-generation targeted anticancer therapies are developed. Effective prevention and management of these photo-induced AEs in cancer patients relies on close collaboration between oncologists and dermatologists. Raising awareness of the photosensitizing potential of anticancer treatments and of the clinical manifestations of photosensitivity are essential for allowing the rapid identification of any further photosensitizing agents and for the prevention of such reactions.

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Data availability statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 Literature search methods.