* TREMFYA® ist indiziert: 1) für erwachsene Patienten mit mittelschwerer bis schwerer **Plaque-Psoriasis**, die für eine systemische Therapie in Frage kommen; 2) allein oder in Kombination mit MTX für die Behandlung der aktiven **Psoriasis-Arthritis** bei erwachsenen Patienten, wenn das Ansprechen auf eine vorherige nicht-biologische krankheitsmodifizierende antirheumatische (DMARD-)Therapie unzureichend gewesen ist oder nicht vertragen wurde.[1]

\# PASI 90: 84% (Wo 48; n=534) Non Responder Imputation (NRI)[2]; PASI 100: 52,7% (Wo 252; n=391) Treatment Failure Rules (TFR)[3]; Signifikante Überlegenheit vs. Placebo in Bezug auf ACR20 (64% vs. 33%, p<0,0001; NRI) nach 24 Wochen in der 8-Wochen-Dosierung (n=248) in bionaiven Patienten mit aktiver PsA.[4]

1. Aktuelle Fachinformation TREMFYA®. **2.** Reich K et al. Lancet. 2019;394(10201):831–839. **3.** Reich K et al. Br J Dermatol. 2021 Jun 9. doi: 10.1111/bjd.20568.
4. Mease P et al. The Lancet 2020; https://doi.org/10.1016/S0140-6736(20)30263-4 (Supplementary)

▼ Dieses Arzneimittel unterliegt einer zusätzlichen Überwachung. Daher ist es wichtig, jeden Verdacht auf Nebenwirkungen in Verbindung mit diesem Arzneimittel zu melden.

TREMFYA® 100 mg Injektionslösung in einer Fertigspritze/ in einem Fertigpen. Wirkstoff: Guselkumab. **Zusammensetz.:** Fertigspritze/Fertigpen enth. 100 mg Guselkumab. Sonst. Bestandt.: Histidin, Histidinmonohydrochlorid-Monohydrat, Polysorbat 80, Sucrose, Wasser f. Injektionszw.. **Anw.geb.:** Für d. Bhdlg. erw. Pat. m. mittelschwerer bis schwerer Plaque-Psoriasis indiziert, d. für e. syst. Therapie in Frage kommen. Als Monotherapie od. in Komb. m. Methotrexat für d. Bhdlg. erw. Pat. m. Psoriasis-Arthritis indiziert, d. auf e. vorherige nicht-biolog. krankheitsmodifiz. antirheumat. (DMARD)-Therapie unzureich. angesprochen od. diese nicht vertragen haben. **Gegenanz.:** Schwerwieg. Überempfindl. gg. Guselkumab od. e. d. sonst. Bestandt., klin. relev. aktive Infektionen (einschl. aktive Tuberkulose), Schwangersch., Stillzeit. **Bes. Warnhinw. u. Vorsichtsmaßn.:** Um d. Rückverfolgbark. b. biolog. Arzneim. zu verbessern, sollten Name u. Ch.-Bez. d. verabreich. Prod. deutl. protokoll. werden. Vors. b. Infektionen, Tuberkulose, Impfungen (vor Anw. v. Lebendimpfst. muss d. Bhdlg. m. Tremfya nach d. letzt. Gabe f. mind. 12 Wo. ausgesetzt werden). B. Erhöh. v. Leberenzymwerten (ALT/AST) u. Verdacht auf arzneimittelinduz. Leberschädig. sollte d. Bhdlg. vorüberg. unterbr. werden. B. schwerwieg. Überempfindl.reakt. sollte d. Anw. v. Tremfya unverzügl. abgebrochen u. e. geeign. Bhdlg. eingel. werden. Frauen im gebärfäh. Alter sollen währ. u. f. mind. 12 Wo. nach d. Bhdlg. e. zuverlässig. Verhütgs.meth. anw.. Arzneim. f. Kdr. unzugängl. aufbewahren. **Nebenwirk.:** *Sehr häufig* (≥ 1/10), *Häufig* (≥ 1/100 bis < 1/10), *Gelegentlich* (≥ 1/1.000 bis < 1/100). *Sehr häufig:* Atemwegsinfekt.. *Häufig:* Kopfschm., Diarrhoe, Arthralgie, Reakt. a. d. Injektionsst., Transamin. erhöht. *Gelegentlich:* Herpes-simpl-Infekt., Tinea-Infekt., Gastroenteritis, Überempfindl.reakt., Anaphylaxie, Urtikaria, Hautausschlag, Neutrophilenzahl erniedr.. Verschreibungspflichtig. **Pharmazeut. Unternehmer:** JANSSEN-CILAG International NV, Turnhoutseweg 30, B-2340 Beerse, Belgien. **Örtl. Vertreter für Deutschland:** Janssen-Cilag GmbH, Johnson & Johnson Platz 1, D-41470 Neuss. **Stand d. Inform.:** 12/2020.

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Research in practice: Therapeutic targeting of oncogenic *GNAQ* mutations in uveal melanoma

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Summary

Uveal melanoma is the most common form of eye cancer and has a poor prognosis. Although the primary tumor in most cases is treated effectively by local surgery or radiotherapy, over 50 % of patients develop systemic metastasis, especially in the liver. In contrast to cutaneous melanoma, there is no standard-of-care treatment for metastasized uveal melanoma. Recently, oncogenic driver mutations in *GNAQ* or *GNA11* were identified in about 85 % of uveal melanomas, which lead to constitutively active signaling in the $G\alpha_{q/11}$ pathway and its downstream effectors. Direct targeting of deregulated $G\alpha_{q/11}$ signaling might therefore be a therapeutic option for patients with uveal melanoma. In our study we identified the cyclic depsipeptide FR-900359, which is isolated from the evergreen plant *Ardisia crenata* as an effective inhibitor of constitutively active $G\alpha_{q/11}$ proteins and their downstream targets. Although our data are preliminary, they might contribute to a future treatment option for patients with metastasized uveal melanoma.

Clinical problem

The uvea is the pigmented middle layer of the eye, consisting of choroid, ciliary body and iris. About 85 % of uveal melanomas (UM) start in the choroid, while tumors of the ciliary body (5–8 %) and iris (3–5 %) are rare. Even though uveal melanoma is the most common form of eye cancer in adults, its incidence worldwide is only estimated at four cases per million [1], and it only accounts for 3–5 % of all melanoma subtypes. Risk factors for developing uveal melanoma are similar to those for cutaneous melanomas, and include intensity of sun exposure, fair skin, light eye color as well as the presence of uveal nevi [2]. Usually UMs appear in older people with a peak of around 70 years, but young adults or even children can also be affected [3]. In most cases, the primary tumor is controlled well with radiotherapy, local extraction or enucleation. Nevertheless, about 50 % of patients develop systemic metastasis, predominantly in the liver (90 %) but also in the lungs, skin or bone [4–6]. In contrast to cutaneous melanoma, there is no standard-of-care treatment for metastasized UM. Systemic chemotherapy or local treatment of hepatic metastasis (e.g. surgery or hepatic perfusion) have few benefits and no changes in overall survival [7]. The prognosis for metastatic UM therefore remains poor with a median survival of twelve months.

Hypothesis

G-protein-coupled receptors (GPCRs) comprise a large family of cell-surface receptors that transduce signals via interaction with heterotrimeric G-protein subunits (Gα, Gβ, and Gγ). The aberrant expression, overexpression and signal reprogramming of GPCRs and G-proteins have been linked to cancer initiation, tumor cell growth, metastasis and angiogenesis. The important role of GPCR-$G\alpha_q$ signaling in melanocyte neoplasia became apparent with the discovery of somatic *GNAQ* or *GNA11* mutations in blue melanocytic nevi in the skin and in about 85 % of uveal melanomas [8, 9]. These genes encode for the heterotrimeric G protein α subunits, $G\alpha_q$ and $G\alpha_{11}$. Oncogenic driver mutations appear exclusively in the residues Q209 and R183, both leading to constitutively active signaling in the $G\alpha_q$ pathway and its downstream effectors. In contrast, normal melanocytic nevi and melanomas originating from epidermal melanocytes frequently carry oncogenic mutations in *BRAF*, *NRAS* and *NF1* but only very rarely in *GNAQ* or *GNA11*. Direct targeting of

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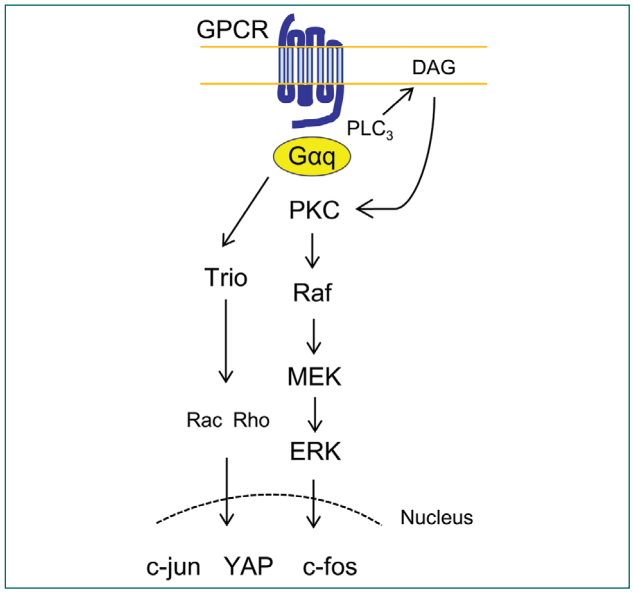

Figure 1 Schematic picture of a G-protein coupled receptor (GPCR) signaling pathway. $G\alpha_q$ proteins activate phospholipase C (PLC) β, leading to generation of the second messenger diacylglycerol (DAG). DAG activates classic protein kinase C (PKC) isoforms, which then stimulate MAPK signaling (Raf-MEK-ERK), a central pathway for aberrant cell growth and cell survival in malignant disease. GPCR signaling also drives the invasion and metastasis of cancer cells via recruitment of the guanine nucleotide exchange factor Trio, resulting in the sustained activation of the small GTPases Rho and Rac and their downstream targets, including the transcription factors and co-activators JUN, FOS and YAP.

deregulated $G\alpha_{q/11}$ signaling might be a therapeutic option for patients with uveal melanoma (Figure 1). Only two selective Gq/11-inhibitors, FR-900359 and YM-254890, are of potential interest for targeting oncogenic signaling [10, 11].

Research for clinical practice

Experiments with human uveal melanoma cell lines and in xenograft mouse models were primarily used to target effector pathways downstream of $G\alpha_q$ and $G\alpha_{11}$, including protein kinase C (PKC), mitogen activated protein kinases (MAPK) and Yes-associated protein (YAP). These effectors regulate cell functions such as proliferation, migration and apoptosis, which are known to play a central role in oncogenesis. Although *in vitro* and *in vivo* experiments showed inhibitory effects of PKC, MEK or YAP blockade on uveal melanoma growth [12, 13], clinical trials with the MEK inhibitor selumetinib and the PKC inhibitor AEB071 only reported limited effects on progression-free survival and no effect on overall survival [14, 15]. YAP inhibition with verteporfin was limited due to high cytotoxicity rates [16]. Inhibition of constitutively active $G\alpha_q$ mutants may represent a new and effective molecular intervention that targets oncogenic signaling in uveal melanoma.

We initially investigated the possibility of therapeutic inhibition of aberrant $G\alpha_q$ activity in the murine melanoma cell line HCmel12. This cell line was derived from a primary melanoma established in the genetic HGF-Cdk4^{R24C} mouse melanoma model, in which the transgenic expression of hepatocyte growth factor (HGF) provides constitutive signaling via the receptor tyrosine kinase c-Met, and thus activates several intracellular signaling pathways including RAS-MAPK and PI3K-AKT. HGF-Cdk4^{R24C} mice develop spontaneous skin melanomas that metastasize to the lymph nodes and lungs [17–19]. In an initial screening for somatic genomic mutations in HCmel12 cells we unexpectedly identified the oncogenic mutation $G\alpha_{11}^{Q209L}$, but mutations in *BRAF* or *NRAS* were not detected. Together with the group of Prof. Evi Kostenis we showed that the cyclic depsipeptide FR-900359, which was already identified in 1998 in the leaves of the plant *Ardisia crenata* [20], is a potent selective Gq/11-inhibitor (Figures 2, 3). Our experiments revealed that FR-900359 strongly inhibited a variety of cell functions associated with oncogenesis, including proliferation, metabolism and migration of HCmel12 melanoma cells [11, 21].

Figure 2 The evergreen plant *Ardisia crenata* (image kindly provided by Dr. M. Crüsemann, Institute for Pharmaceutical Biology, University of Bonn).

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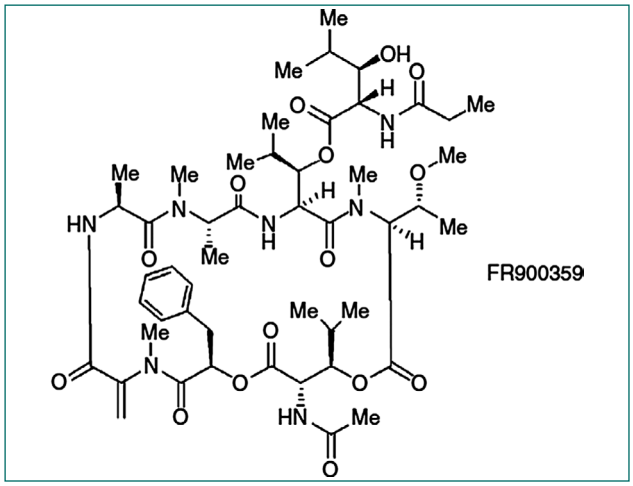

Figure 3 Chemical structure of FR-900359 [21].

The effect of FR-900359 on GNA_{11}^{Q209L} mutated murine melanoma cells was completely unexpected. Current literature suggests that FR-900359 functions as a $G\alpha_q$-specific guanine nucleotide dissociation inhibitor (GDI) that binds to the GDP-bound form of Gαβ/γ Gq heterotrimers and keeps them in an inactivated state [22, 23]. Mutations in Gα proteins lead to constitutive activation, for example by impairing the intrinsic ability to hydrolyze GTP [24]. Therefore, FR-900359 should only affect signaling by wild type but not by mutated $G\alpha_q$. In subsequent experiments on human uveal melanoma cell lines with $G\alpha_{q/11}$ mutations (Mel270, Mel202, Mel92.1 and OMM1.3) we also found that FR-900359 specifically blocked effector pathways downstream of $G\alpha_q$ and $G\alpha_{11}$ (including ERK and YAP) and inhibited the proliferation of mutated UM cells. In contrast, wild type $G\alpha_{q/11}$ UM cell lines (Mel285 and Mel290) were unaffected by FR-900359 treatment. FR-900359 also significantly suppressed tumor growth in a mouse xenograft model driven by mutant $G\alpha_q^{Q209P}$. The control, a human melanoma cell line carrying a mutant B-Raf^{V600E}, showed progressive growth. Our findings were consistent with two other in vitro studies, which described inhibitory effects of FR-900359 on mutated uveal melanoma cell lines [24, 25].

The unexpected observation that oncogenic but not wild type Gq proteins can be inhibited pharmacologically was further clarified by Annala et al [21]. In general, GPCR signal transduction involves the activation of heterotrimeric G proteins via the release of GDP and binding of GTP. The Gα subunit then dissociates from the Gβ and Gγ subunits, and all G protein components are then able to activate different downstream effectors. GPCR-Gα signaling is deactivated again by hydrolysis of GTP to GDP. Since GDP release is slow in comparison to GTP hydrolysis, the number of activated Gα subunits is controlled by the amount of agonist-occupied GPCRs. Oncogenic Gq proteins are constitutively active. In this situation, the actual hydrolysis rate from GTP to GDP is too slow to reset GDP-Gα. Therefore, the nucleotide state of mutated Gq is more dependent on nucleotide concentration than on ligand-activated GPCRs. Annala et al. showed that inhibitors of nucleotide dissociation such as FR-900359 shift the equilibrium towards inactive GαGDP-βγ heterotrimers, thus accumulating inactive G proteins over time. Consequently, downstream signaling pathways of $G\alpha_q$ and $G\alpha_{11}$ are blocked [21, 26].

Conclusions for clinical practice

Our findings demonstrate that murine and human uveal melanoma cell lines carrying mutated $G\alpha_q$ proteins can be significantly inhibited by the cyclic depsipeptide FR-900359 *in vitro* and *in vivo*. Since standard-of-care therapies for cutaneous melanoma (including agents such as MEK inhibitors) are not effective with metastasized uveal melanoma, our data may contribute to a new treatment option with selective targeting of mutationally activated $G\alpha_{11}$ and $G\alpha_q$ proteins. However, several open questions still need to be addressed, such as the detailed pharmacodynamics and pharmacokinetics of FR-900359.

Author

Evelyn Gaffal works at the Department of Dermatology at the University Hospital of Magdeburg Germany. She is currently president of the German Society of Investigative Dermatology. Her research interests include molecular mechanisms in the pathogenesis and therapy of malignant melanoma and the regulation of inflammatory immune responses in the skin.

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metex® PEN 7,5 mg / 10 mg / 12,5 mg / 15 mg / 17,5 mg / 20 mg / 22,5 mg / 25 mg/ 27,5 mg / 30 mg Injektionslösung im Fertigpen. *Wirkstoff:* Methotrexat-Dinatrium. **Zusammensetzung:** 1 Fertigpen mit 0,15 ml/ 0,20 ml/ 0,25 ml/ 0,30 ml/ 0,35 ml / 0,40 ml/ 0,45 ml/ 0,50 ml/ 0,55 ml/ 0,60 ml Lösung enthält 7,5 mg/ 10 mg/ 12,5 mg/ 15 mg/ 17,5 mg/ 20 mg/ 22,5 mg/ 25 mg/ 27,5 mg/ 30 mg Methotrexat. *Sonstige Bestandteile:* Natriumchlorid, Natriumhydroxid-Lösung 5%, Salzsäure 0,37%, Wasser für Injektionszwecke. **Anwendungsgebiete:** Aktive rheumatoide Arthritis bei erwachsenen Patienten; polyarthritische Formen von schwerer aktiver juveniler idiopathischer Arthritis (JIA), wenn das Ansprechen auf nicht-steroidale Antirheumatika (NSAR) nicht ausreichend war; mittelschwere bis schwere Psoriasis vulgaris bei erwachsenen Patienten, die für systemische Therapieformen in Frage kommen, sowie schwere Psoriasis arthropathica bei Erwachsenen; leichter bis mittelschwerer Morbus Crohn, entweder allein oder in Kombination mit Kortikosteroiden bei Erwachsenen, die auf Thiopurine nicht ansprechen oder diese nicht vertragen. **Gegenanzeigen:** Überempfindlichkeit gegen Methotrexat oder einen der sonstigen Bestandteile; schwere Leberfunktionsstörungen; Alkoholabusus; schwere Nierenfunktionsstörungen (Kreatinin-Clearance unter 30ml/min); vorbestehende Blutbildveränderungen wie Knochenmarkshypoplasie, Leukopenie, Thrombozytopenie oder signifikante Anämie; schwere, akute oder chronische Infektionen wie Tuberkulose, HIV oder andere Immundefizienzsyndrome; Ulzera der Mundhöhle und bekannte Ulzera des Magen-Darm-Traktes; Schwangerschaft, Stillzeit; gleichzeitige Impfung mit Lebendimpfstoffen. **Warnhinweis:** metex PEN (Methotrexat) darf zur Behandlung von rheumatoider Arthritis, juveniler idiopathischer Arthritis, Psoriasis, Psoriasis arthropathica und Morbus Crohn nur einmal wöchentlich angewendet werden. 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Immunsystem: Selten:* Allergische Reaktionen, ansphylaktischer Schock, Hypogammaglobulinämie. *Stoffwechsel, Ernährung: Gelegentlich:* Manifestation eines Diabetes mellitus. *Psychiatrisch: Gelegentlich:* Depressionen, Verwirrtheit. *Selten:* Stimmungsschwankungen. *Nervensystem: Häufig:* Kopfschmerzen, Müdigkeit, Verschlafenheit. *Gelegentlich:* Schwindel. *Sehr selten:* Schmerzen, Muskelschwäche oder Parästhesie/ Hypoästhesie, Geschmacksveränderungen (metallischer Geschmack), Krampfanfälle, Meningismus, akute aseptische Meningitis, Lähmungen. Enzephalopathie/ Leukenzephalopathie *(Häufigkeit nicht bekannt). Augen: Selten:* Sehstörungen. *Sehr selten:* Sehverschlechterung, Retinopathie. *Herz: Selten:* Perikarditis, Perikarderguss, Perikardtamponade. *Gefäße: Selten:* Hypotonie, thromboembolische Ereignisse. *Atemwege, Brustraum, Mediastinum: Häufig:* Pneumonie, interstitielle Alveolitis/Pneumonitis, oft verbunden mit Eosinophilie. Symptome, die auf potenziell schwere Lungenschädigungen (interstitielle Pneumonitis) hinweisen: trockener Reizhusten, Kurzatmigkeit, Fieber. *Selten:* Lungenfibrose, Pneumocystis-jirovecii-Pneumonie, Kurzatmigkeit, Asthma bronchiale, Pleuraerguss. Epistaxis, pulmonale alveoläre Blutung *(Häufigkeit nicht bekannt). Gastrointestinaltrakt: Sehr häufig:* Stomatitis, Dyspepsie, Übelkeit, Appetitlosigkeit, abdominelle Schmerzen. *Häufig:* Ulzerationen der Mundschleimhaut, Diarrhö. *Gelegentlich:* Ulzerationen und Blutungen des Magen-Darm-Traktes, Enteritis, Erbrechen, Pankreatitis. *Selten:* Gingivitis. *Sehr selten:* Hämatemesis, Hämatorrhö, toxisches Megakolon. *Leber, Galle: Sehr häufig:* Abnorme Leberfunktionswerte (ALAT, ASAT, alkalische Phosphatase und Bilirubin erhöht). *Gelegentlich:* Leberzirrhose, Leberfibrose, Leberverfettung. Verminderung von Serumalbumin. *Selten:* Akute Hepatitis. *Sehr selten:* Leberversagen. *Haut, Unterhaut: Häufig:* Exantheme, Erytheme, Pruritus. *Gelegentlich:* Photosensibilität, Haarausfall, Zunahme von Rheumaknoten, Hautulzera, Herpes Zoster, Vaskulitis, herpetiforme Hauteruptionen, Urtikaria. *Selten:* Verstärkte Pigmentierung, Akne, Petechien, Ekchymose, allergische Vaskulitis. *Sehr selten:* Stevens-Johnson-Syndrom, toxische epidermale Nekrolyse (Lyell-Syndrom), verstärkte Pigmentierung der Nägel, akute Paronychie, Furunkulose, Teleangiektasie. Exfoliation der Haut/ exfoliative Dermatitis *(Häufigkeit nicht bekannt). Skelettmuskulatur, Bindegewebe, Knochen: Gelegentlich:* Arthralgie, Myalgie, Osteoporose. *Selten:* Stressfraktur. Osteonekrose des Kiefers, sekundär zu lymphoproliferativen Erkrankungen *(Häufigkeit nicht bekannt). Niere, Harnwege: Gelegentlich:* Entzündungen und Ulzerationen der Harnblase, Nierenfunktionsstörungen, Miktionsstörungen. *Selten:* Niereninsuffizienz, Oligurie, Anurie, Elektrolytstörungen. Proteinurie *(Häufigkeit nicht bekannt). Geschlechtsorgane, Brustdrüse: Gelegentlich:* Entzündungen und Ulzerationen der Vagina. *Sehr selten:* Libidoverlust, Impotenz, Gynäkomastie, Oligospermie, Menstruationsstörungen, vaginaler Ausfluss. *Allgemein, Verabreichungsort: Selten:* Fieber, Wundheilungsstörungen. Asthenie. Nekrose an der Injektionsstelle, Ödem *(Häufigkeit nicht bekannt).* Subkutane Anwendung von MTX ist lokal gut verträglich; nur leichte örtliche Hautreaktionen wie Brennen, Erythem, Schwellung, Verfärbung, Pruritus, starker Juckreiz, Schmerzen, die im Laufe der Behandlung abnehmen. *Verschreibungspflichtig.* **medac GmbH,** Theaterstr. 6, 22880 Wedel, Deutschland. **Stand** November 2021