Topical Chemotherapy of Skin Cancers

SEYYED MASOUD DAVOUDI M.D.

TEHRAN UNIVERSITY OF MEDICAL SCIENCES

Review Article

Mediators of Inflammation in Topical Therapy of Skin Cancers

Vlad Mihai Voiculescu,[1,2] **Cristina Victoria Lisievici**,[1] **Mihai Lupu**,[2,3] **Cristina Vajaitu**,[1] **Carmen Cristina Draghici**,[1] **Alexandra Victoria Popa**,[1] **Iulia Solomon**,[1] **Teona Ioana Sebe**,[2,4] **Maria Magdalena Constantin**,[2,5] **and Constantin Caruntu**[2,6]

[1]*Department of Dermatology, "ELIAS" University Emergency Hospital, Bucharest, Romania*
[2]*Carol Davila University of Medicine and Pharmacy Bucharest, Romania, Bucharest, Romania*
[3]*Dermatology Clinic, MedAs Medical Center, Bucharest, Romania*
[4]*The Clinic of Plastic Surgery Reconstructive Microsurgery, Emergency Hospital Bucharest, Romania*
[5]*2nd Department of Dermatology, "Colentina" Clinical Hospital, Bucharest, Romania*
[6]*Department of Dermatology, Prof. "N Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest, Romania*

Correspondence should be addressed to Maria Magdalena Constantin; drmagdadinu@yahoo.com

- Current literature confirms the idea that cancer may develop under specific environments generated by chronic inflammation.

Treatment of skin cancers

Although surgical treatment is the gold standard therapy for skin cancers, being chosen in 95% of the cases, a large range of other options has developed

Treatments for melanoma, in turn, are primarily surgical because these tumors can be resistant to traditional chemo- and radiotherapies

Nonsurgical treatments for melanomas are limited to adjuvant therapies, such as immunotherapy, biochemotherapy, gene therapy and photodynamic therapy

- To increase patient compliance and to reduce surgical costs and undesirable scars, particularly in cases where the cancer has spread over large areas of the body, the topical administration of anticancer drugs has been investigated.
- The topical administration of anticancer drugs is an interesting alternative for reducing side effects and for increasing drug targeting and therapeutic benefits.
- The major challenge of this kind of treatment is to increase penetration of the antineoplastic tumor drug in sufficient levels to kill tumor cells.

- Several techniques and formulations have therefore been developed to successfully overcome skin barriers and to reach skin malignancies by favoring drug penetration into the deep layers of the epidermis.
- The use of **chemical penetration enhancers** is the simplest strategy, causing temporary and reversible disruption of the stratum corneum bilayers and leading to increased anticancer drug penetration into the tumor.
- Moreover, great interest has been shown in **nanoparticle delivery** systems that can protect anticancer drugs against degradation and, combined with physical methods, significantly increase the tumor penetration of the drug.

Drug penetration in the skin

- Development of skin tumors is associated with many factors, but most of these cancers are related to excess ultraviolet radiation (UV) exposure.
- Following sun exposure-induced damage, the stratum corneum of tumor lesions usually presents with hyperkeratinization , a factor known to hamper drug penetration.
- Topical anticancer administration therefore requires a well-designed formulation to increase drug penetration into the thicker stratum corneum and to favor drug penetration into the deep skin layers, where tumors are usually located.

- For example, the most superficial malignancy that develops in the epidermis is actinic keratosis, so-named because of the exaggerated production of keratin in the stratum corneum, which causes it to become thicker.
- These lesions can develop into tumors, usually SCCs, which may be nodular (invasive) and hyperkeratotic.
- For topical treatment of both actinic keratosis and SCC, anticancer drugs should penetrate the stratum corneum to reach the tumor cells.

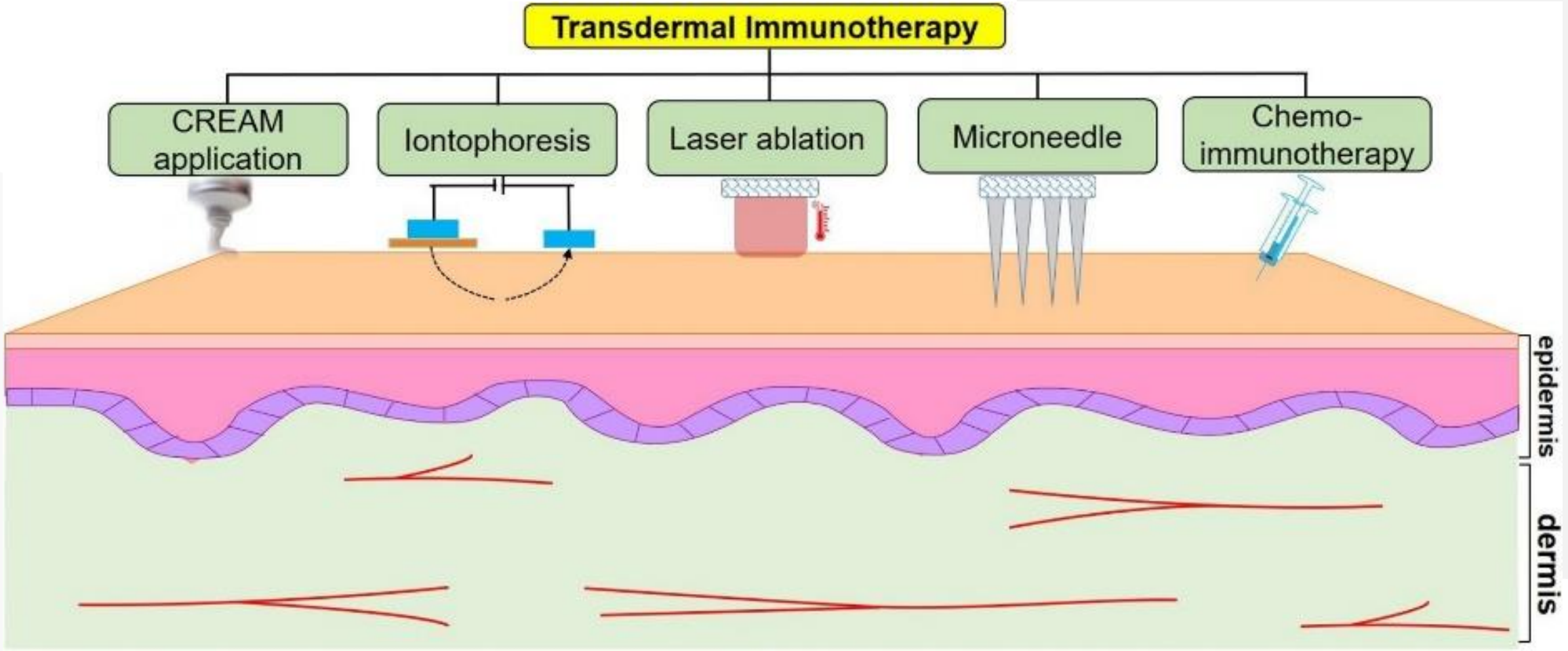
$$J = \frac{\mathrm{Dm\ Cv}\ P}{\mathrm{L}},$$

- Drug permeation through the stratum corneum can be described with **Ficks's second law**
- where ***J*** is the flux, **Dm** is the diffusion coefficient of the drug in the membrane, **Cv** is the drug concentration in the vehicle, ***P*** is the drug partition coefficient and ***L*** is the stratum corneum thickness.

1. **Chemical penetration enhancers**
2. **Physical penetration method**

such as **iontophoresis** and **electroporation**, may alter one or more of these parameters to increase drug penetration in the skin.

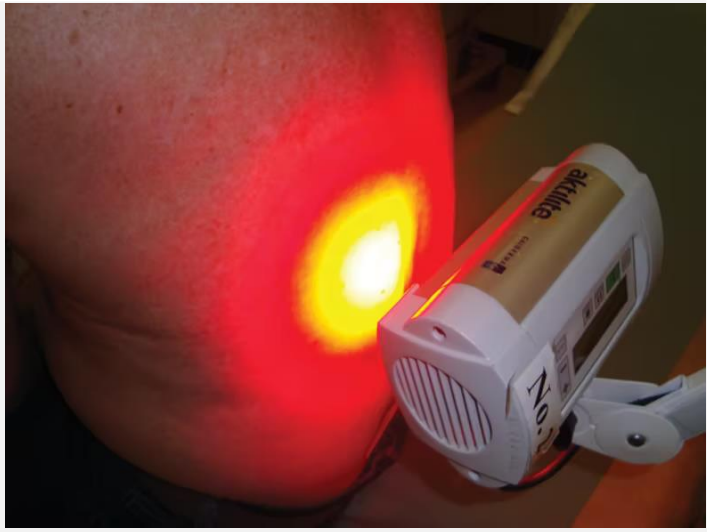
- For instance, **chemical enhancers** can disrupt the stratum corneum barrier and increase the diffusion coefficient of the drug through the altered membranes.
- Alternatively, enhancers can alter the solvent nature of the skin and improve partitioning between the formulation and the stratum corneum.
- **Nanocarriers** can increase drug concentration in the vehicle and so increase drug flux.
- **Physical penetration methods** can modify drug penetration routes through the stratum corneum, making it less tortuous, facilitating drug penetration


Transdermal Immunotherapy
CREAM application
Iontophoresis
Laser ablation
Microneedle
Chemo-immunotherapy
epidermis
dermis

- Treatment options for localized skin cancers include the following:

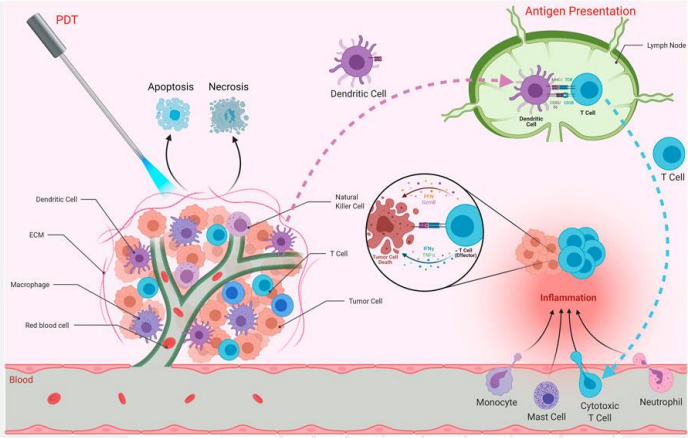
- Surgical excision with margin evaluation
- Mohs micrographic surgery
- Radiation therapy
- Curettage and electrodesiccation
- Cryosurgery
- Carbon dioxide laser
- **Photodynamic therapy**
- **Topical Chemotherapy**

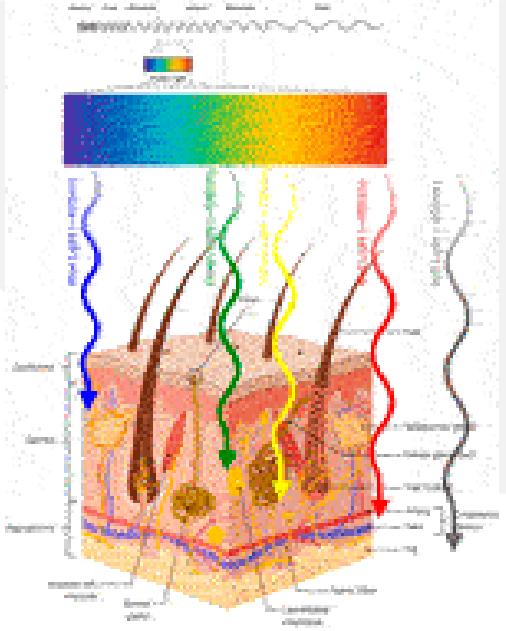
Photodynamic therapy



- A topical photosensitizing agent such as **5-aminolevulinic acid** or **methyl aminolevulinate** is applied to the tumor, followed by exposure to a specific wavelength of light (laser or broad band).
- In the case of multiple BCCs, the use of short-acting systemic (intravenous) photosensitizers such as **verteporfin** has been investigated.
- Upon light activation, the photosensitizer reacts with oxygen in the tissue to form singlet oxygen species, resulting in local cell destruction.

1. PDT can affect immune responses and induce anti-tumor immunity.
2. PDT may result in apoptosis and/or necrosis of the tumor cells.
3. It is also capable of inducing immunogenic cell death, which stimulates immune responses against dead cell antigens.

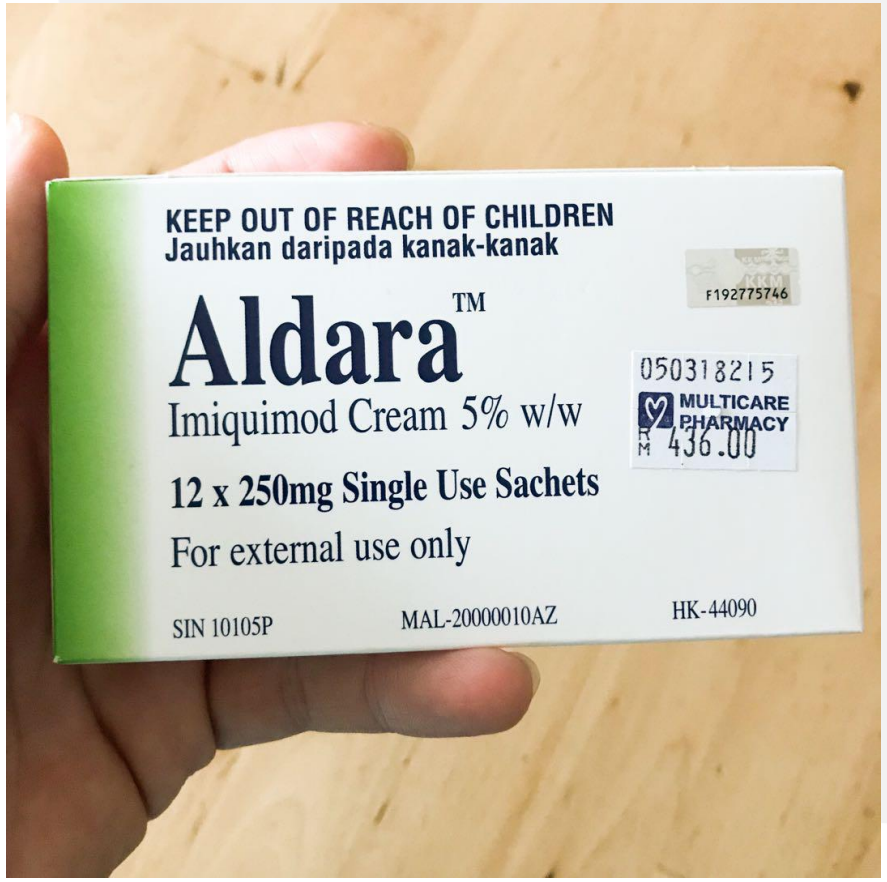




The antigens are taken up by antigen presenting cells such as dendritic cells. Activated T cells as well as monocytes, mast cells and neutrophils are recruited to the tumor microenvironment, resulting in inflammation. Effector T cells are capable of eliminating tumor cells.

Current topical therapies for skin cancer treatment

Imiquimod


KEEP OUT OF REACH OF CHILDREN
Jauhkan daripada kanak-kanak
F192775746
Aldara™
Imiquimod Cream 5% w/w
050318215
MULTICARE PHARMACY
436.00
12 x 250mg Single Use Sachets
For external use only
SIN 10105P
MAL-20000010AZ
HK-44090

- **Imiquimod (IMQ)** is a novel synthetic compound and member of the imidazoquinoline family that binds to TLR-7 and -8, determining high levels of interferon-alpha (IFN-α), tumor necrosis factor alpha (TNF-α), and other interleukins (IL-6, IL-8, etc.).

- It has been suggested that IMQ activates Langerhans cell migration and determines contact hypersensitivity by stimulating cytokine expression and, as a result, enhances antigen presentation

Imiquimod and Actinic keratosis

- When facing a patient with multiple AKs, the treatment of choice is the "field treatment," using PDT therapy, topical chemotherapy, and immunotherapy, this way also treating subclinical AKs.
- A phase II study showed that **topical IMQ 5%, applied 1-3 times/week**, significantly reduced the number and dimension of AKs.
- There were minimal adverse reactions, the therapy being better tolerated than other topical/surgical treatments in use.
- Studies have also shown that the higher the inflammation induced by IMQ, the faster the AKs are eradicated

- However, until more information is available, it is sugessted that surgical treatment or radiotherapy remains the recommended therapeutic option for such potentially aggressive tumors, because there is a risk of incomplete clearance.
- Currently,the recommendations are two applications/week forabout 16 weeks, but it may vary

Imiquimod and SCC

- In situ SCC can be really hard to differentiate from AK, and the fact that the mechanism of healing includes the same paths when treated with topical IMQ 5% means that topical therapy might be a valid alternative to surgical excision
- A couple of published case reports and small series have documented IMQ's off-label use in the treatment of in situ SCC, Bowenoid papulosis, extramammary Paget's disease, melanoma in situ, cutaneous metastases of melanoma, keratoacanthoma, and others

- A recent case report presented two cases of SCC treated with once daily application of 5% IMQ cream for 6 weeks.
- The first patient presented two months later with a subcutaneous nodule, which was histologically diagnosed as recurrent SCC, and after five months following the excision he developed metastatic SCC to a cervical lymph node.
- The second patient had low-grade chronic lymphocytic leukaemia with SCC in situ of the leg that failed to clear clinically at the end of the IMQ treatment, and after 4 months he re-presented with a focus of invasive SCC within the lesion.In this second case, there was a theoretical potential for failure of immune upregulation with IMQ therapy in immunosuppressed patients.
- Nonetheless, in the largest study to date, there was a complete clinical and histological response in 14 out of 15 patients with SCC in situ after IMQ topical treatment, once daily for 6 weeks

Imiquimod and Melanoma

- It has been reported that IMQ may upregulate gene expression of endogenous angiogenesis inhibitors in melanoma tissue .
- Off-label, topical IMQ is suggested as an alternative treatment to melanoma surgery and also as an adjunctive therapy after surgery.
- Topical IMQ has been used recently in the treatment of melanoma in situ and also cutaneous melanoma metastases.
- One case report concluded that 5% IMQ may be used in combination with topical 5-FU in cases of melanoma metastases

- Recent studies demonstrated the use of IMQ as an adjunctive therapy for melanoma alongside radiotherapy, by enhancing cell death through autophagy. An overexpression of the autophagy-related genes and also a large number of autophagosomes.
- This study states that IMQ may be used as a radiosensitizer and immune booster alongside radiotherapy for melanoma cases

- IMQ alone or in combination with intralesional IL-2 may be a promising immunomodulatory treatment as adjuvant topical treatment for patients with multiple cutaneous melanoma metastases .
- Some studies suggest that the association between IMQ and BCG (Bacillus Calmette-Guérin) vaccine induces systemic anti-melanoma immunity.
- There is a phase II, single- centre, randomized pilot study which started in 2017, regarding the use of topical IMQ or diphenylcyclopropenone for the management of cutaneous melanoma metastases .

- Recent studies suggest that IMQ is also very useful in diseases associated with pathological neovascularization such as dysplastic nevi, melanoma, NMSCs, Kaposi’s sarcoma, hemangioma of infancy, pyogenic granuloma, and angiosarcoma, as an inhibitor of angiogenesis.
- The advantages of the use of topical IMQ are that it is self-applied, it is a nonscarring procedure, and it is less expensive and less painful. Moreover, it can be used as an alternative on sensitive areas or lesions that involve large areas which are not susceptible to surgery

Imiquimod and BCC

- A recent study has demonstrated that regression of BCC is associated with the activity of the innate immune response.
- Activation of the innate immune system cells and release of oxygen reactive intermediates and other toxic molecules, all of this leading to the apoptosis of tumoral cells.
- They also suggested that this mechanism is related to destruction of the overlying epithelial cells resulting in typical erosions observed during IMQ treatment.
- An important observation is that T cell activation occurred later during treatment, suggesting that this is not the main factor during tumoral cell elimination

- The treatment of superficial BCC implies a regimen of 5 applications/week for 6 weeks (5% IMQ cream). This application rate has proven to histologically eradicate a superficial BCC up to 82% at a 3-month follow-up and 89% at a 39-month follow-up.
- A 5-year follow-up revealed that there were no recurrences, years after topical treatment with IMQ, in BCC lesions.

An exhaustive review of the literature confirmed that cryotherapy, photodynamic therapy (PDT), topical IMQ, and 5-FU are valid alternatives for low-risk superficial BCCs

- Other studies show that

1. Topical IMQ 5% therapy has superior success rates than 5-FU and PDT(even though there seems to be no link between tumor thickness and success rate regarding the three options mentioned above)
2. IMQ is more efficient in BCCs localized on the face compared to the ones on the trunk (which is reassuring considering the high recurrence rate of facial BCC)
3. There is no correlation between the severity of the reactions at the application site (itching, crusting) and the response rate.
4. There is a positive association between the dosing frequency and the response rate,and also the occurrence of local side effects.
5. Occlusion of the skin after IMQ application does not enhance the efficacy, but instead it may produce severe side effects

- Bostanci et al. have proposed the use of IMQ not only for superficial BCC, for which it is approved, but also for other histological subtypes, with good long-term cosmetic results.The authors included tumors greater than 1cm in diameter with various subtypes, including aggressive variants (infiltrative, metatypical, and solid).
- A recent trial which compared the surgical results versus IMQ 5% cream in patients with nodular and superficial BCC concluded that although surgery was superior, IMQ also showed promising results.

- The histologic clearance rate was more than 80% among nodular BCCs larger than 1cm in diameter. However, for nasal localization of the BCC, the results were not as satisfactory, with a long-term response of only 63%.
- Therefore, the authors suggest IMQ treatment of **nasal BCCs** only if the patient cannot tolerate other types of treatment.
- After a mean follow-up of 70 months, only 2 relapses were observed among 21 patients with complete response. These 2 relapses were diagnosed with metatypical pathology. Metatypical BCC is a rare subtype of BCC, characterized by both basaloid and squamoid differentiation.

- The authors suggested that IMQ treatment should be avoided in metatypical carcinoma, due to its aggressive biology. Usually, the prognosis for this type of carcinoma is worse than for the classical BCC, and the recurrence rate is higher.
- The vast majority of recurrences of the BCC occurred within the first 12-24 months.

- There is some evidence in the literature that IMQ can be successfully used in the treatment of some sclerodermiform and infiltrative types of BCC and may induce partial remission of multiple BCCs in patients with **Gorlin syndrome** or **xeroderma pigmentosum**

Ingenol mebutate (IM)

- Ingenol mebutate (IM) is an agent extracted from the sap of Euphorbia peplus, a plant which has been used in the past by Romans and Greeks , and is recently used in the treatment of various skin diseases such as warts and AK. This molecule was approved for the treatment of AK in 2012, therefore being among the newer topical therapies for skin cancer.
- It is suggested that there are multiple mechanisms of action, including direct cell death and a complex inflammatory response, mediated partially by **PK-C (protein kinase C)** activation.
- It seems that IM stimulates the production of tumor-specific antibodies and proinflammatory cytokines, therefore inducing cellular cytotoxicity and preventing recurrence

- IM dissolves into the cell membrane and induces a rise in the intracytoplasmic calcium level which then induces mitochondrial destruction .
- After topical application, it produces a neutrophilic infiltration, due to the PK-C activation .
- The importance of **neutrophils** in sustaining tumor-free skin is evidenced by a study which showed that in neutrophil-depleted mice, although clearance of the tumor was achieved after 3 days of treatment, the recurrence appeared after 25 days

- Topical administration of IM induces the destruction of epidermis, the new epidermis showing significant reduction in keratinocytes expressing p53 mutated gene .
- It has also been discovered that skin which has not been exposed to UV radiation is less susceptible to develop erythema after topical administration of IM.
- The mechanism is unknown at the moment, but it is believed that normal skin may not be as permeable to this molecule as sun-damaged skin; also, in normal skin, mast-cell degranulation is lower than in chronic UV-exposed skin

Ingenol Mebutate and BCC

- IM gel therapy has proved its efficiency without important side effects in the treatment of pigmented and nonpigmented superficial BCC.
- In a phase IIa trial which evaluated its use in the treatment of superficial BCC, only the highest concentration (0.05%) administered on consecutive days was statistically more efficient than the vehicle.
- **Additional trials are needed because the indications for BCC treatment are currently off-label**

Ingenol Mebutate and AK

- Another recent study on the pharmacodynamics of IM, and looking at the local changes in both normal skin and in AK lesions on which they applied the drug, suggested that a strong inflammatory response was noted in both instances.
- Therefore, IM gel 0.05% is capable of inducing epidermal cell death and also immune reactions .
- The current treatment recommendations are one application of 0.05% or 0.015% gel/day for 2-3 consecutive days

- Phase 3 studies showed its efficiency in clearing AK, with sustained clearance over 12 months, using concentrations of 0.015% for face and scalp and 0.05% for trunk and extremities.
- There is evidence to suggest that IM has higher efficacy than diclofenac 3% and IMQ 5% in the treatment of AK.
- A case report showed full clinical remission of multiple AKs with good aesthetic outcome in a patient with organ transplant, which used IM on large skin areas.
- This suggests that IM may be used on large areas, even on 100 cm2 of skin, resembling field cancerization treatment by photodynamic therapy without the systemic side effects

Ingenol Mebutate and SCC

- Another situation in which IM may be of use is the treatment of multiple SCC in patients with organ transplant, where field cancerization is common, because the immunosuppression promotes keratinocyte tumoral formation and decreases the immunity.
- Erlendsson et al. have concluded that repeated field-directed treatments with IM delay the development of UV-related SCC in hairless mice.
- The authors also noticed that increased local skin reactions including erythema, flaking, crusting, vesiculation, swelling, and ulceration are associated to improved clinical outcomes. Currently, it is used off-label in the treatment of SCC

Ingenol Mebutate and Mycosis Fungoides

- **A 2016 study concluded that topical IM 0.05% may be an effective alternative topical treatment for localized plaques/patches of mycosis fungoides (MF) and folliculotropic MF.**
- It must however be taken into consideration that patients included in this trial were also receiving systemic methotrexate.
- The authors supposed that the mechanism of action is based on the PMN (polymorphonuclear neutrophil) oxidative burst and keratinocyte cytokine release and, nonetheless, apoptosis.
- Studies have shown that the adherence to IM therapy is higher than with other topical molecules, due to the shorter treatment duration

Nonsteroidal Anti-inflammatory Agents and NMSCs

- Topical therapy with nonsteroidal anti-inflammatory agents (NSAIDs) has proven to induce apoptosis, and it seems that there is a very strong link between cyclooxygenase2(COX2) activity and the expression of antiapoptotic proteins.
- COX exists in two forms, COX1 and COX2; the first is constitutively expressed, while the second is expressed after inflammatory stimuli, like ultraviolet light exposure The overexpression of COX2 has been revealed in numerous neoplasms, including skin cancer.

- Normal skin has low levels of COX2 and PGE2 (prostaglandin E2), but these levels increase with the severity of the malignancy.
- Recent studies suggest the importance of COX2 and its products, especially PGE2, in the development of NMSC.
- Studies show positive results after treatment with NSAIDs for different types of cancer. The main mechanism of action is the inhibition of angiogenesis and the stimulation of apoptosis through COX2 inhibition.

- Diclofenac, a NSAID, reduces the production of prostaglandins by inhibiting the formation of COX2, thereby reducing dysplastic keratinocytes in cancerous lesions.

- Currently, it is approved for the treatment of AK, twice-daily application, for 2-3 months. It can be used including in solid organ transplant recipients, but there are no data regarding its efficacy for BCC or SCC.

- Two case series have reported clearance of **Bowen's disease** in a total of 7 patients treated with topical diclofenac for 56 to 90 days. Further studies should be conducted before it can be recommended as treatment for NMSC.
- Diclofenac also seems to be a valid therapy option for melanoma skin metastases.

- Currently, the formula containing 3% diclofenac in 2.5% hyaluronic acid has been approved for the treatment of AK , its efficacy ranging from 38% to 47% complete clinical clearance of AKs in different studies

Combined therapy

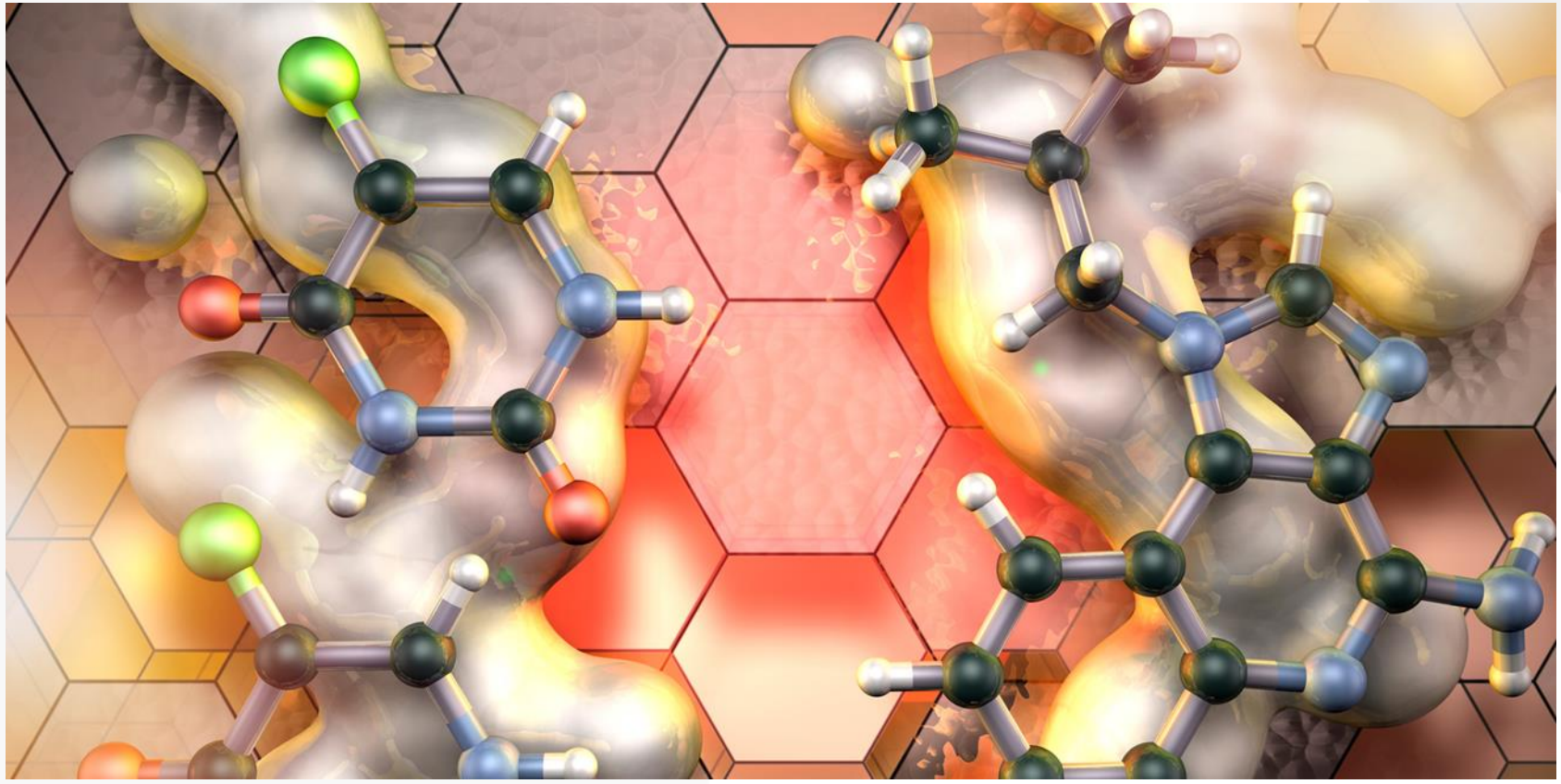
- It has been shown that the efficacy of IMQ can be accentuated by combined therapy with ipilimumab (a CTLA-4 specific antibody) has shown promising results in metastatic melanoma patients
- Associated with systemic acitretin, topical IMQ 5% seems to reduce the recurrence of superficial BCC, more than IMQ 5% cream used alone.
- Rausch et al. showed that IMQ induces a delay in tumor growth and it does not contribute to any memory formation, but by combining it with other immune stimulants like UV-light and CD40 ligands, this inconvenience might be solved
- 5-FU may be applied to the lesion alongside tretinoin cream, which enhances its actions

Novel Therapies and Future Directions

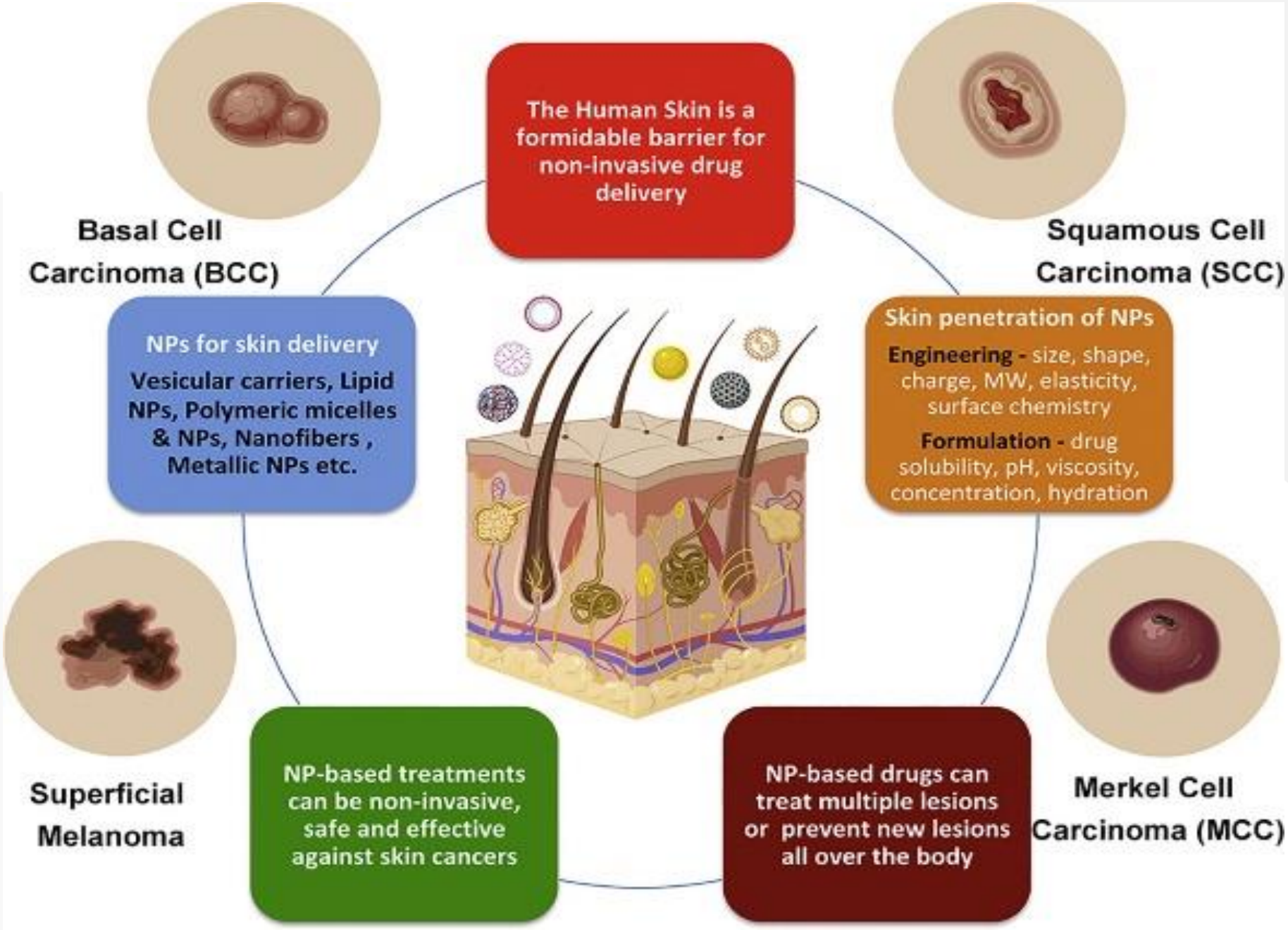
- **Imidazoquinoline**, similar to IMQ, which activates TLR-7 with highly selectivity, is currently being investigated for the treatment of various neoplasms, including inoperable melanoma .
- Preclinical studies have also demonstrated that IMQ and **resiquimod** amplify the antitumoral effect of some vaccines by stimulating the innate immune system, but further investigation should be conducted in order to find novel therapies targeting TLR

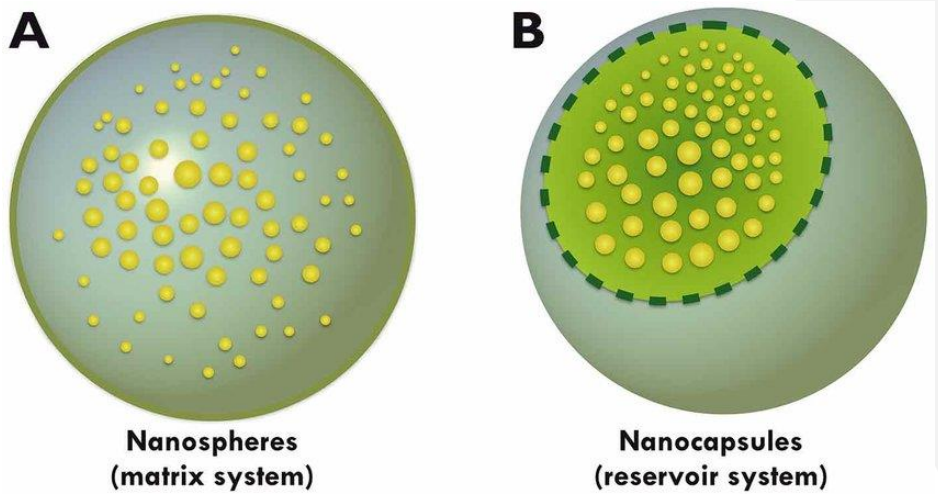
- Further directions should also be oriented towards the **bacterial enzyme T4N5 endonuclease**, which repairs UVA-damaged DNA.
- It is a local therapy which was used to treat diseases such as xeroderma pigmentosum, AKs, and BCCs, reducing the lesions.
- This enzyme is able to minimize the production of cutaneous IL-10 and TNF-alpha and also to restore the interferon-gamma-induced ICAM-1expression in the skin

Role of Polymeric Nano Particles for the Effective Treatment of Skin Cancer



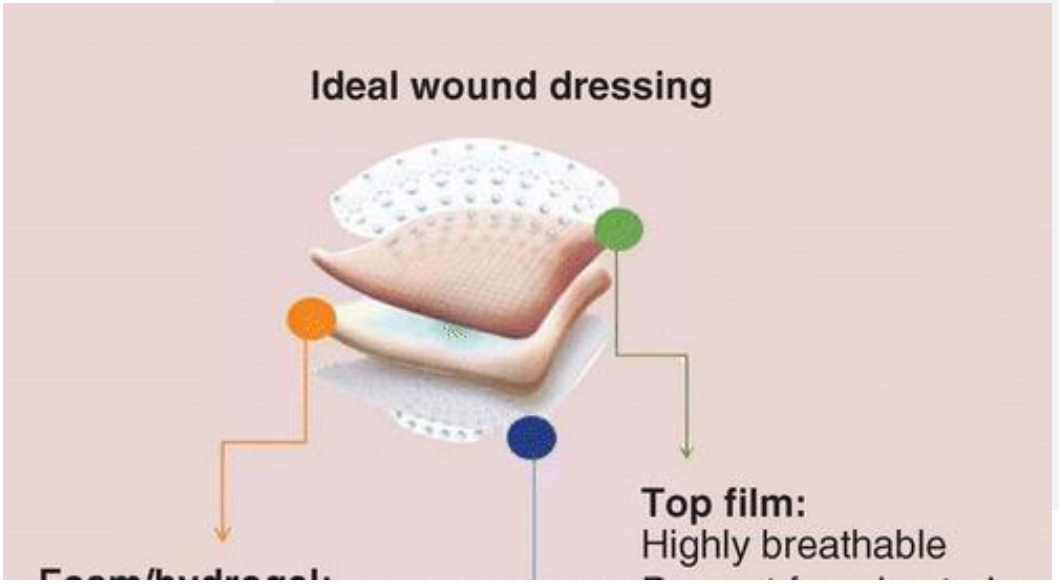
- Nano particles is used for the delivery of a controlled and sustained dosage of a skin cancer drug through the skin over a period of time.
- The polymeric nano particles offers various advantages over the skin cancer increased solubility, sustain release, penetrability, specific site of action and reduced dose for therapeutic effect.


The Human Skin is a formidable barrier for non-invasive drug delivery
Basal Cell Carcinoma (BCC)
Squamous Cell Carcinoma (SCC)
NPs for skin delivery
Vesicular carriers, Lipid NPs, Polymeric micelles & NPs, Nanofibers , Metallic NPs etc.
Skin penetration of NPs
Engineering - size, shape, charge, MW, elasticity, surface chemistry
Formulation - drug solubility, pH, viscosity, concentration, hydration
Superficial Melanoma
Merkel Cell Carcinoma (MCC)
NP-based treatments can be non-invasive, safe and effective against skin cancers
NP-based drugs can treat multiple lesions or prevent new lesions all over the body



- Many types of polymeric nanoparticles including both synthetic and semisynthetic have been reported in literature in treating various diseases including cancers.
- The nano particles is generally defined as solid, colloidal particles in the range between 10-1000 nm. The term polymeric nano particle is collective term which is given for any type of polymer nano particle(specific type's nano-spheres and nano-capsules).

Regenerative Wound Dressings for Skin Cancer



- For skin cancer treatment, radical tumor excision remains the most effective approach among the available strategies.
- post-surgery management should involve the application of wound dressings for promoting skin regeneration and preventing tumor recurrence and microbial infections, which still represents a considerable clinical challenge.
- Therefore, wound dressings consisting of biopolymers as the regenerative component and natural anti-cancer agents as the cancer recurrence-preventing component could represent ideal candidates to use for regenerative applications in skin cancer.

Laser-assisted delivery enhances topical uptake of the anticancer agent cisplatin

- Systemic chemotherapy with the anticancer agent **cisplatin** is approved for advanced non-melanoma skin cancer (NMSC), but topical treatment is limited by insufficient cutaneous penetration.
- Ablative fractional laser (AFL) provides rapid, greatly increased and uniform delivery of the anticancer agent cisplatin deep into full thickness skin.
- Improved cutaneous uptake of this potent chemotherapeutic may prove useful in the development of a new, local and minimally-invasive treatment for dermatological neoplasms.

THANK YOU FOR YOUR ATTENTION

WWW.ARGANO.IR

TEHRAN UNIVERSITY OF MEDICAL SCIENCES