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Journal

Seminars in Cutaneous Medicine and Surgery, 36(4)

ISSN

1085-5629

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Publication Date

2017-12-01

DOI

10.12788/j.sder.2017.044

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State-of-the-art lasers and light treatments for vascular lesions: from red faces to vascular malformations

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Abstract

Notable milestones in the treatment of vascular lesions have been achieved over the past century. Many cutaneous vascular lesions can be successfully treated with light-based devices. In this review, we will discuss the treatment of port-wine birthmarks, lymphatic malformations, infantile hemangiomas, rosacea, venous lakes, pyogenic granulomas, cherry angiomas, and angiofibromas using lasers, total reflection amplification of spontaneous emission of radiation, intense pulsed light, and photodynamic therapy. In addition, for several of these diagnoses, we will review medical therapies that can be combined with light-based devices to provide enhanced results.

Semin Cutan Med Surg 36:207-212 © 2017 Frontline Medical Communications

For centuries, light has played an important role for the treatment of skin conditions. Physicians in ancient Egypt used sunlight and natural psoralens for the treatment of vitiligo. Cutaneous tuberculosis was treated successfully with Finsen light therapy at the end of the 19th century. In 1925, Goeckerman introduced ultraviolet B light therapy and the application of crude coal tar to treat psoriasis with marked results.

Lasers originated after the theory of stimulating radiant energy developed in the 20th century. In 1916, Albert Einstein proposed that a photon of electromagnetic energy could prompt the delivery of another identical photon from atoms or molecules that are in an excited state. This theory led a Californian group headed by the physicist Theodore Maiman to the invention of the first laser in 1959.[1-3] The pioneering work of the dermatologist Leon Goldman pushed laser devices into the dermatological practice. A ruby laser emitting light at 694 nm was introduced first; thereafter, the 488- to 514-nm argon lasers were developed[1] and used to treat vascular lesions.[3] In the 1980s, Anderson and Parrish introduced the concept of selective photothermolysis,[4] allowing targeting of chromophores without damage to surrounding skin structures. This greatly decreased adverse effects, including scarring, and increased the therapeutic potential of these devices. In the 1990s, epidermal cooling was introduced,[5] which allowed the safer use of higher fluences and treatment of patients with darker skin types.

Light-based devices are currently the standard of care treatment for many cutaneous vascular lesions. Our aim in this review is to provide an update for the applications of lasers and other light-based devices for cutaneous vascular lesions. We will discuss light treatment of port-wine birthmarks (PWBs), lymphatic malformations (LMs), infantile hemangiomas (IHs), rosacea/telangiectasias, venous lakes (VLs), pyogenic granulomas (PGs), cherry angiomas, and angiofibromas. We will also discuss combinations of light sources and medications that may provide enhanced results (Table).

Vascular malformations

Port-wine birthmarks

PWBs are venous capillary vascular malformations present in up to 0.5% of the population. Approximately 162 million individuals in the United States are affected with PWBs.[6,7]

PWBs appear at birth as pink-to-erythematous flat patches. Over time, tissue may hypertrophy, the color may darken to deep red or purple, and nodules may develop.[6] Histologically, numerous dilated capillaries are seen throughout the dermis. PWBs can be part of Sturge-Weber syndrome (SWS), in which some or all of the following features may be present: a facial PWB, a proliferation of capillaries in the eye, and ipsilateral brain angiomata (leptomeningeal angiomata). Patients affected by SWS may present with developmental delays and seizures.[8] Other PWB-associated syndromes include Klippel-Trenaunay, Cobb, and Proteus.[6]

Somatic mutations in the Guanine nucleotide-binding protein G(q) subunit alpha (GNAQ) gene have been found in a significant number of SWS and nonsyndromic PWB. This mutation has been shown to activate extracellular signal-regulated kinases (ERKs). ERKs and c-Jun N-terminal kinase may contribute to the pathogenesis and progressive development of PWBs. Activation of protein kinase B (also known as AKT) and phosphatidylinositol 3-kinase is implicated in promoting hypertrophic PWBs. Phosphoinositide phospholipase C γ subunit may participate in the formation of nodules.[9] Investigations on other mutated candidate genes are ongoing.[10]

Laser devices are the gold standard for the treatment of PWBs.[11] The 595-nm pulsed-dye laser (PDL) is a device commonly used to treat PWBs, and with good response. However, approximately 20% of PWB patients are nonresponsive to PDL, in part because good response to PDL may depend on sufficient light penetration, which may be lacking in deep/thick PWBs and in lesions with scarring from previous treatments.[12] Nonresponders may be treated with lasers of different wavelengths, such as the combined 595/1064-nm device, and intense pulsed light (IPL). The long-pulsed 755-nm laser is another useful alternative, achieving deeper light penetration with a preferential absorption by deoxyhemoglobin.[12]

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Disclosures: Dr Valdebran and Dr Martin have nothing to disclose. Dr Kelly reports personal fees and nonfinancial support from Syneron - Candela , nonfinancial support from Light Sciences Oncology, personal fees from MundiPharma, personal fees from Allergan, nonfinancial support from Sciton, nonfinancial support from ThermiRF, during the conduct of the study.
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1085-5629/13$-see front matter © 2017 Frontline Medical Communications
DOI: https://doi.org/10.12788/j.sder.2017.044

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Early treatment

Treating PWB at a young age may achieve enhanced results,[6] in part because of the increased hemoglobin concentrations during the first year of life, which are attributed to hemoglobin F and may serve as an additional target in these very young patients. The presence of thinner skin and smaller PWB vessels in this population may also contribute to the enhanced response of treatment compared with older individuals.

Photodynamic therapy

Photodynamic therapy (PDT) uses exogenous photosensitizing drugs activated by certain wavelengths of light to cause photoreactions. The transfer of energy from the activated photosensitizer to oxygen molecules produces highly reactive singlet oxygen capable of irreversible oxidation of essential cellular components, which leads to apoptosis and cellular death.[13] Experiments with animal models using PDT to target vasculature were performed in

TABLE Summary of light treatments for vascular lesions

Condition	Key notes	Light therapy	Medical therapy used alone or in combination with light therapy
Port-wine birthmarks	Vascular malformation GNAQ gene mutation Associated with Sturge-Weber, Klippel-Trenaunay, Cobb, and Proteus syndromes	532-nm KTP 595-nm PDL PDL + radiofrequency 755-nm Alexandrite Photodynamic therapy	Rapamycin Axitinib
Microcystic lymphatic malformation	Lymphangioma circumscriptum Dilated lymphatic channels in the upper dermis Amenable to treat with laser	Fractionated 10600-nm CO_2 laser Fractional Er:YAG laser Continuous wave Nd:YAG	Topical rapamycin
Infantile hemangiomas	Vascular tumor Early treatment minimizes the risk of complications	595-nm PDL	Oral or topical beta-blocker
Rosacea	Inappropriate response to environmental stimuli leading to induction of the innate immune system and overstimulation of the sensory and autonomic nervous system	IPL 532-nm KTP 595-nm PDL 595-nm Q-switched Nd:YAG TRASER	Topical adrenergic agonists: oxymetazoline
Venous lakes	Dilated thin-walled venules in the papillary dermis Typically seen in the lower lip	595-nm PDL 755-nm Alexandrite 800-nm diode laser 1064-nm Nd:YAG	
Pyogenic granulomas	Exophytic and lobular proliferation of small capillaries associated with a fibrous stroma	595 nm PDL 1064-nm Nd:YAG	
Cherry angiomas	Dilated and congested capillaries in the papillary dermis	532-nm KTP 595-nm PDL 1064-nm Nd:YAG	
Angiofibromas	Can be associated with tuberous sclerosis complex in which multiple hamartomas develop in the skin and other organs including the brain, kidneys, lungs, heart and eyes	532-nm KTP 595-nm PDL Fractionated 10600-nm CO_2 laser	Topical rapamycin Topical timolol

Abbreviations: CO_2, carbon dioxide; Er:YAG, erbium-doped yttrium aluminium garnet; GNAQ, guanine nucleotide-binding protein G (q) subunit alpha (Gαq); IPL, intense pulsed light; KTP, potassium titanyl phosphate; Nd-YAG, neodymium-doped yttrium aluminium garnet; PDL, pulsed dye laser; TRASER, total reflection amplification of spontaneous emission of radiation.

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the 1980s.[14-16] Since the 1990s, Chinese clinicians have performed PDT for PWBs by using the long-pulsed 532-nm potassium titanyl phosphate (KTP) and 510- or 578-nm copper vapor lasers in combination with photosensitizers such as photocarcinorin. Gu et al reported clearance of 50% and above in more than 90% of their patients in a series of 1942 PWBs treated with PDT.[17,18] In a retrospective analysis of 238 PWB cases, Qin et al reported complete clearance or marked blanching with flatter lesions and no initial scarring in 60.5% of the patients. Side effects included self-limited hyperpigmentation in 72% of the patients, secondary scars in 2 patients, and phototoxicity in 1 patient.[19]

Although hematoporphyrin photosensitizers can be effective for PWBs, photosensitivity lasting up to a week is a major limiting factor. As such, alternative photosensitizers have been considered.[20] Our group explored PDT with benzoporphyrin derivative monoacid ring A and 576-nm light, which has the advantage of a relatively short 5-day photosensitivity period. We also combined PDT (irradiance of 100 mW/cm^2 and doses up to 90 J/cm^2) with PDL (7 mm spot, 1.5-ms pulse duration, fluence of 8 J/cm^2), which allows for a synergistic treatment effect and a decrease in the risk of adverse effects. Improved efficacy was noted in the PDT combined with PDL site compared with PDT or PDL alone. No major adverse effects were found with carefully planned intervention and epidermal changes were limited to fine scabbing and temporary mild hyperpigmentation at PDL-treated sites.[21] Recently, we explored talaporfin sodium (photosensitive period: 7-10 days) in combination with red light (664 nm). Significant PDT effect could be achieved, but there was a risk of deep injury when higher fluences were used. In order to safely use PDT, it is our opinion that an objective end point must be identified, allowing for desired vascular damage without damage to the surrounding skin.[22]

Pulsed-dye laser in combination with radiofrequency

Bae et al recently investigated the utility of combining PDL with radiofrequency (RF) for treatment of recalcitrant PWBs in a series of 10 patients. In this technique, RF elevates the temperature in the dermis, helping PDL to reach larger vessels. Areas treated with RF followed by PDL (RF/PDL) and PDL followed by RF showed the greatest improvement ($P < .05$). Histopathological sections from biopsies taken immediately after treatment demonstrated that thermal damage reached a depth of 550 μm in areas treated with RF/PDL. All RF/PDL-treated areas had at least moderate improvement, compared with 60% in the PDL arm. Side effects included purpura, erythema, edema, scabbing, crusting, blistering, and scarring (1 patient). Combined RF/PDL may allow enhanced clearing but must be used cautiously to avoid adverse effects.[23]

Combined laser and antiangiogenic therapy

Another option for patients with resistant PWB is laser vessel destruction followed by antiangiogenic therapy. Rapamycin inhibits the mammalian target of rapamycin (mTOR) pathway, which is involved in protein synthesis, cell proliferation, and angiogenesis. Investigators have studied the use of oral and topical rapamycin in combination with PDL and demonstrated improved outcomes.[24,25] Additional experimental studies have revealed that axitinib suppresses angiogenic stimuli produced by PDL. Axitinib blocks several pathways that include AKT/mTOR/P70S6K and SHC1/MEK/ERK and inhibits several tyrosine kinases such as vascular endothelial growth factor (VEGF) receptors, platelet-derived growth factor receptor, and stem cell factor receptor.[26] Although preliminary studies using antiangiogenic therapy have demonstrated some efficacy in the treatment of PWBs, pathways involved in the maintenance and repair after treatment of PWBs need to be further elucidated. Advances in the characterization of such pathways should lead to the development of additional treatment options.

Lymphatic malformations

LMs are low-flow anomalies of the lymphatic system made up of dilated lymphatic channels lined by endothelial cells without connection with the peripheral lymphatic system.[27-29] The International Society of Vascular Anomalies has classified this entity into microcystic, macrocystic, and mixed LMs.[29] Microcystic LMs, also known as lymphangioma circumscriptum, consist of clusters of translucent or red-purple vesicles, which correspond to dilated lymphatic channels in the upper dermis.[30]

Although fully ablative carbon dioxide (CO_2) lasers have been effectively used in the past to treat these conditions, significant downtime, erythema, and scarring are common side effects. The fractionated 10600-nm CO_2 laser has also been successfully used.[31] A fractionated technique minimizes downtime and adverse effects. Fractional 2940-nm erbium-doped yttrium aluminium garnet and continuous-wave 1064-nm neodymium-doped yttrium aluminium garnet (Nd:YAG) lasers have also been reported to be useful in this condition.[31] Despite progress, recurrence is common, and further research should be done to improve treatment outcomes.

More recently, rapamycin 1% cream applied twice daily was used by Gray et al in an LM on the neck, with positive results after 2 months of treatment.[32] Similar results were communicated by Kim et al when topical rapamycin was applied on the neck and resulted in improvement in LM size and color after 4 months of treatment.[33]

Infantile hemangiomas

IHs are the most common vascular tumors of childhood, presenting in 4% to 5% of white infants and in 1% of Asian and black newborns, with a higher incidence in premature infants weighing less than 1500 g.[34,35] They have an early proliferative phase in the first 6 to 9 months, followed by stabilization and involution, which can last several years.[34,35] After IHs involute, residual lesions can consist of telangiectasias or result in atrophy, scarring, and pigmentary changes. Treatment is used to prevent the compromise of important functions (including vision or feeding), to prevent ulceration, and to avoid long-term disfigurement in cosmetically sensitive areas.[34]

The introduction of oral propranolol has changed the paradigm of the treatment of IHs. Propranolol has proven to be safe and highly effective in the treatment of these vascular lesions. Topical beta-blockers have also been used to minimize systemic side effects of oral preparations. The use of lasers has been recommended for superficial and thin IHs, whereas deep IHs affecting the airways or obstructing the visual field are better treated with oral propranolol. Mixed IHs and refractory superficial IHs may be addressed with a combined treatment.[36]

The 595-nm PDL can be used in the treatment of IHs to slow progression, decrease time to involution, and promote healing in ulcerated lesions. In a retrospective study of 90 patients, treatment with a 595-nm PDL led to 85% clearance of color and 64% reso-

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lution of thickness of the IHs.[37] Besides the coagulative effect of PDL, recent studies have shown that irradiated cells tend to initiate apoptosis and repress the production of VEGF.[35]

Combination of both topical beta blockers and lasers can enhance results for superficial and mixed IH by accelerating treatment response and achieving more complete resolution. Reddy et al retrospectively studied a series of 17 infants with facial-segmental IHs treated with PDL and propranolol; 12 were treated concurrently, 5 were treated with propranolol followed by PDL, and the control group consisted of 8 patients treated with propranolol alone. IHs treated with a combined therapy of propranolol and PDL achieved complete clearance more often and in a shorter time period: a mean of 3 months for concurrent propranolol and PDL versus 6 months for the propranolol followed by PDL group versus almost 10 months for propranolol alone.[38] In a randomized, controlled trial of 30 infants with IHs, topical timolol plus PDL was superior to PDL alone in efficacy, cost benefit, and treatment time for the resolution of IHs.[39]

Rosacea

Rosacea is a chronic inflammatory disorder observed commonly in middle-aged individuals. There are 4 clinical subtypes: (1) erythematotelangiectatic, (2) papulopustular, (3) phymatous, and (4) ocular. The pathophysiology of rosacea is complex. Genetically predisposed individuals respond inappropriately to environmental stimuli, leading to induction of the innate immune system and overstimulation of the sensory and autonomic nervous system, which results in the dysregulation of the function of venules and arterioles. This ultimately leads to chronic inflammation and fibrosis. Clinically, rosacea is characterized by persistent and centrally distributed erythema, telangiectasia, papules, pustules, edema, or a combination of these. Patients can also experience facial flushing, pain, stinging, or burning and, less commonly, pruritus. Initiating or aggravating triggers of rosacea include ultraviolet light, heat, spicy food, alcohol, stress, facial demodex, and small intestine bacterial overgrowth.[40] Histologically, erythematotelangiectatic rosacea shows perivascular and perifollicular inflammatory infiltrate composed mainly of lymphocytes; edema and dilated capillaries may also be observed.[41] Quality of life and self-esteem are frequently affected by this condition, leading to emotional distress and withdrawal from social interactions.[42] Studies have shown that the patient's red face is the main reason medical care is sought. Although medical treatment could help to treat the inflammatory lesions in rosacea, laser and IPL are the most effective means of improving telangiectasias.

PDLs using purpuric settings were the first devices used to successfully treat patients with rosacea. Bruising was a common unwanted side effect; however, the introduction of the long-pulsed PDL allowed minimal bruising while maintaining efficacy. The 595-nm PDL has been extensively used in the treatment of rosacea, resulting in improvements of up to 50% to 75% in telangiectatic vessels in 1 to 3 sessions.[43]

IPL can also be used to treat rosacea. In 1 study, 16 subjects were randomly selected to receive up to 2 split-face treatments onemonth apart, with PDL treatment performed on one side and IPL treatment performed on the other. IPL and PDL modalities resulted in equivalent safety and efficacy outcomes.[44]

The 532-nm KTP laser has been widely used to treat superficial vessels like those present in rosacea. Some KTP lasers can deliver high energies and long pulses of up to 200 ms.[45] Ubelhoer et al published on a series of 15 patients with diffuse telangiectatic facial erythema who were treated with a long-pulsed 532-nm KTP laser on one side of the face and with a 595-nm PDL on the other. The KTP laser group reached 62% clearance after 1 treatment and 85% clearance 3 weeks after the third treatment, compared with 49% and 75% for PDL, respectively. Swelling lasting longer than 1 day was observed in 79% of KTP laser–treated areas versus in 71% of PDL-treated areas. Persistent erythema (for at least 1 day after treatment) was noted in 58% of KTP-treated areas, compared with 8% of PDL-treated areas.[46]

Recently, Goo et al published on the use of a 595-nm Q-switched Nd:YAG laser for treatment of rosacea patients. The 595-nm wavelength is generated by using a handpiece containing a solid dye, which converts the 532-nm beam into a 595-nm beam. Low fluences of 0.4 to 0.5 J/cm^2 allowed only mild pain and discomfort and resulted in rapid resolution of erythema.[47]

Total reflection amplification of spontaneous emission of radiation (TRASER) devices use the light emitted by a flashlamp directed to a fluorescent dye in solution, resulting in spontaneous emission of photons within a narrow wavelength band. Its peak of intensity depends on the characteristics of the selected fluorescent medium, which can be tuned from ultraviolet A to near infrared.[48] Friedman et al reported an improvement greater than 75% in telangiectasias after 1- and 3-month follow-ups after using TRASER treatment for 15 subjects. The most common side effects included edema, erythema, and purpura.[49]

The topical application of α_{1A}-adrenergic agonists such as oxymetazoline has been shown to reduce facial erythema of rosacea by 2 grades or better according to 2 controlled trials.[50] The use of topical α_{1A}-adrenergic agonists may play a role in ameliorating persistent erythema of rosacea in combination with light-based therapies. Studies using combined laser and this new medical therapy are currently underway.

Venous lakes

VLs are venous vascular malformations that commonly affect adult patients and present as soft blue papules in sun-exposed areas, typically on the lower lip. Histologically, they are composed of dilated thin-walled venules and congested vascular channels located in the papillary dermis. Solar damage to the vessel walls and surrounding elastic tissue might play a role in the pathogenesis of VLs.[41,51]

Multiple wavelengths can be used to treat VLs. PDL treatment offers few adverse effects; however, depth of penetration is limited. In VLs with a deep component, the combination of treatment with PDL and the longer-wavelength alexandrite laser has resulted in good outcomes.[52] Wall et al used an 800-nm diode laser and achieved complete clearance of VLs after 1 to 2 treatments.[53]

The long-pulsed 1064-nm Nd:YAG has also been used successfully, although it does have a higher risk of deep thermal damage. Migliari et al used the long-pulsed 1064-nm Nd:YAG on 16 patients with VLs located on the lip and oral mucosa, and this resulted in complete healing 2 to 4 weeks following treatment, with no adverse effects noted.[54] Multiwavelength lasers combining the 595-nm PDL and the long-pulsed 1064-nm Nd:YAG can also be used.[55] Combining wavelengths allows for lower fluences for both

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wavelengths, may improve coagulation, reduces purpura, and decreases patient discomfort.[51]

Pyogenic granulomas

PGs are benign vascular tumors marked by rapid exophytic growth within days to weeks. Histologically, the tumor consists of an exophytic and lobular proliferation of small capillaries associated with a fibrous stroma.[41] The 595-nm PDL may be effective in the treatment of small and flat PGs but is generally not effective in thicker lesions. Hammes et al reported using the long-pulsed 1064-nm Nd:YAG laser. After 1 to 4 sessions, 19 of 20 patients were recurrence-free with no visible textural changes.[56]

Cherry angiomas

Cherry angiomas present clinically as multiple red papules on the trunk and limbs of middle-aged or elderly individuals. Histologically, they are characterized by dilated and congested capillaries in the papillary dermis.[41] Treatment options include the long-pulsed 532-nm KTP, 595-nm PDL, and long-pulsed 1064-nm Nd:YAG lasers. In a series of 45 patients, Pancar et al reported that 2 comparable lesions from the same patient were treated by using different modalities, one by using KTP laser and the other by using Nd:YAG. Both lasers were found to be effective. Erythema, edema, pain, and scar formation were higher in the Nd:YAG group, whereas hyperpigmentation was the main side effect in the KTP group and therefore should be used with caution in dark-skinned patients.[57]

Angiofibromas

Tuberous sclerosis complex (TSC) is a genetic disorder with a prevalence of 1 in 1600 births. Although this is an autosomal dominant condition, de novo mutations are present in two-thirds of patients. Mutations in *TSC1* and *TSC2* cause dysregulation of mTOR signaling giving rise to uncontrolled cell proliferation. As a consequence, multiple hamartomas develop in the skin and other organs.[58] Male individuals with *TSC2* mutations tend to have more severe clinical manifestations.[59]

The most common dermatologic complaint is the presence of angiofibromas, which can appear shortly after birth and consist of erythematous papules typically located in the central face. These are highly visible and may cause emotional distress.

Several options have been described to treat angiofibromas. PDL treatment may help to lessen erythema, but this alone may not clear lesions fully. Papular fibrosis can be targeted with ablative devices, including the ablative fractional laser (AFL). Topical rapamycin, an inhibitor of mTOR, has been reported to improve angiofibromas. In a case report, Bae-Harboe and Geronemus successfully used a combination of 595-nm PDL followed by an AFL for treatment. Electrosurgery was also performed on papular lesions, with topical 0.2% rapamycin applied twice daily starting immediately postprocedure and continued until follow-up at 3 months. This combination of therapies safely and effectively treated angiofibromas associated with tuberous sclerosis.[60] Park and colleagues have reported on a small series of cases in which topical therapy of 0.1% rapamycin was started for 2 to 3 months, followed by ablative laser therapy for larger (>4 mm), poorly responsive papules. This combination appeared useful for treating larger angiofibromas and preventing recurrences after laser treatment.[61]

Krakowski and Nguyen reported treating angiofibromas by using a 595-nm PDL followed by a macrofractionated 10600-nm CO_2 laser. Starting on the 5th postoperative day, topical 0.5% timolol was applied on the right cheek. Four months later, the timolol-treated area exhibited reduced numbers of papules and less erythema.[62]

Conclusion

Light-based devices have allowed for successful treatment of a wide range of cutaneous vascular lesions including PWBs, microcystic LMs, IHs, rosacea/telangiectasias, VLs, PGs, cherry angiomas, and angiofibromas. These devices, alone and in combination with medical therapy, have aided in the improvement of the quality of life of patients afflicted with vascular malformations and tumors. Although the field of laser surgery has witnessed much progress in the light-based treatment of vascular lesions, continued research and curiosity are needed to perfect and improve upon these advances.

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