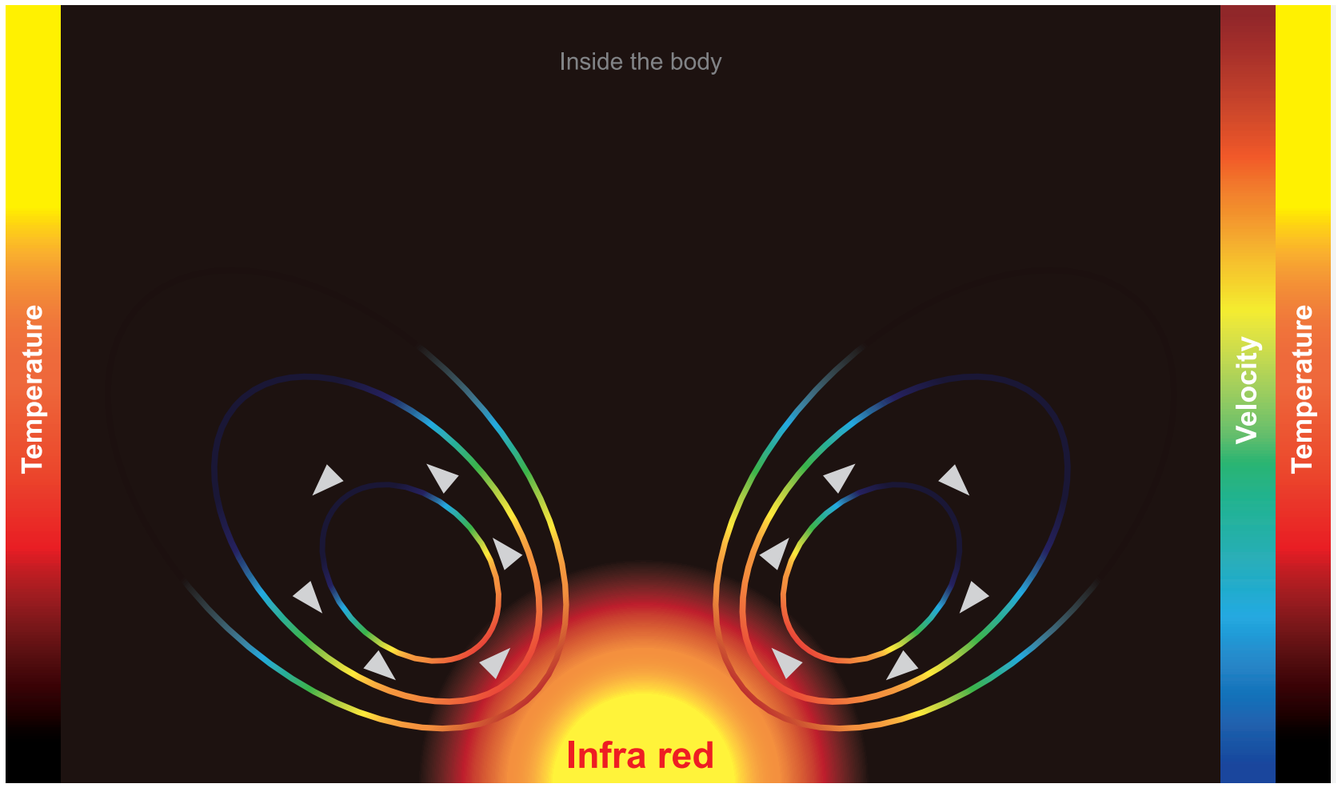
Reference

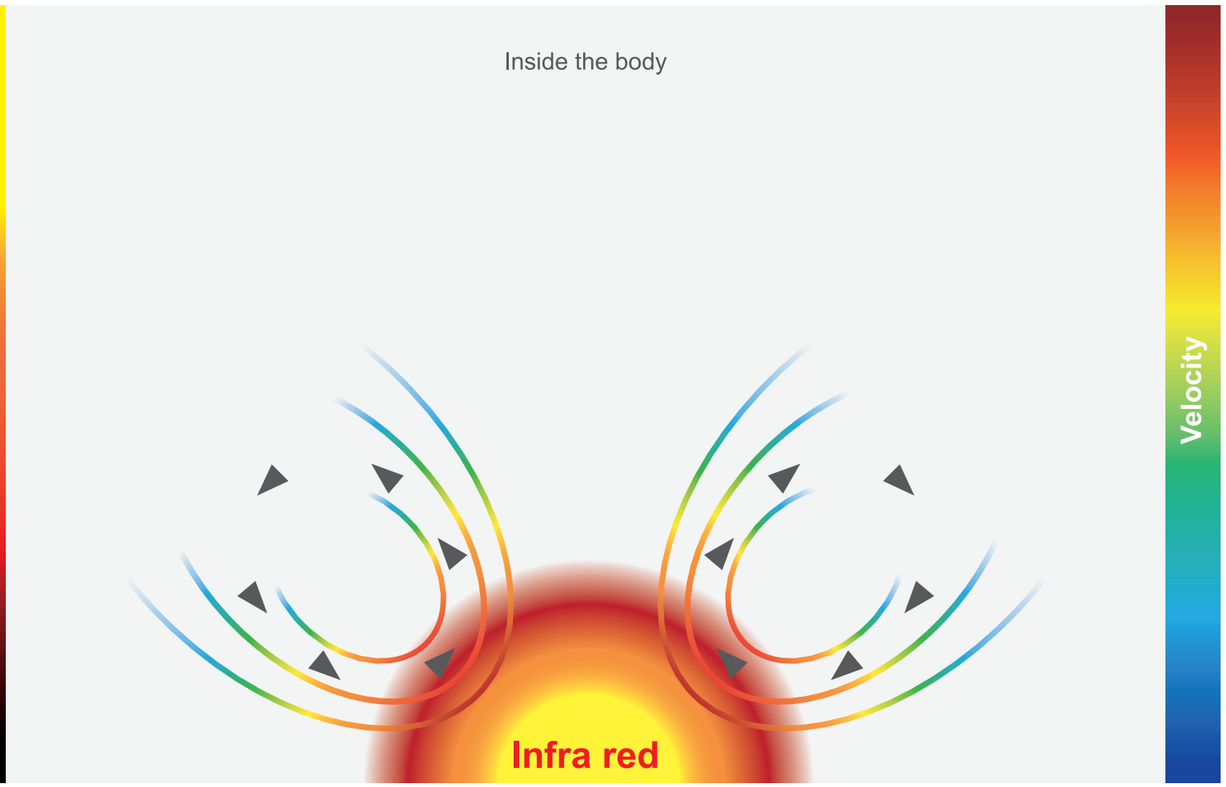
特 許 出 願 中

実 用 新 案 取 得 済

Ray Balance

Ray Balance Technology





[製造・販売元]

・東京都港区三田3-4-3 506
・AKT VISION 株式会社
・TEL：03-5324-2791
・URL

[開発会社]

・東京都港区南青山3-9-1
・日商平野株式会社
・Http://www.nisshomh.jp

ISOに於ける赤外線

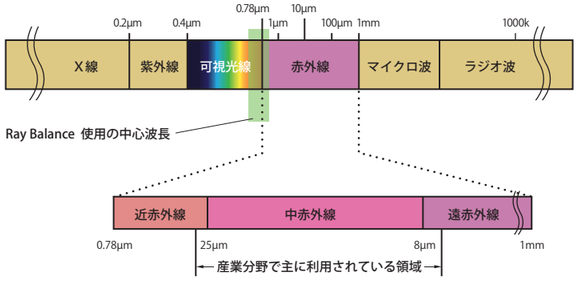
Near Infra red	0.78−3.0μm
Mid Infra red	3.0−50.0μm
Far Infra red	50.0−1000.0μm

一般的な赤外線の波長区分について

Near Infra red	0.78−2.5μm
Mid Infra red	2.5−8.0μm
Far Infra red	8.0−1000.0μm

Ray Balance使用の波長

IR PEAK 波長	855nm
可視光 PEAK 波長	630nm



近赤外線について

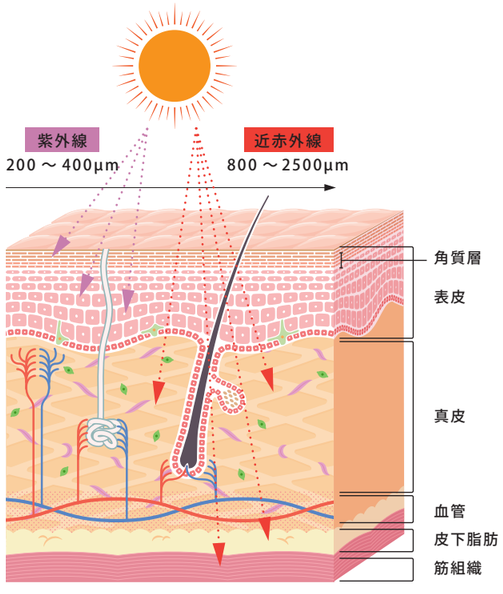
近赤外線は、医療や美容等の分野に於いて広く利用されていますが、近年は特に医療分野での利用が拡大されていると言われております。PBM：Photobiomodulation（フォトバイオモデュレーション：光による生体調整）やLLLT：Low Level Light Therapy（ローレベルライトセラピー：低線量光治療）といった言葉が広く知られるるようになってきています。では何故、近赤外線が利用されているのでしょうか？

それは、近赤外線の生体深達度が高いため、表面だけでなくある程度の深さの細胞にまで作用する事が出来る為であると考えられています。

[そもそも近赤外線とは？]

・おおよそ 800 ～ 2500μm の波長帯

・太陽光線の５０％以上を占める！

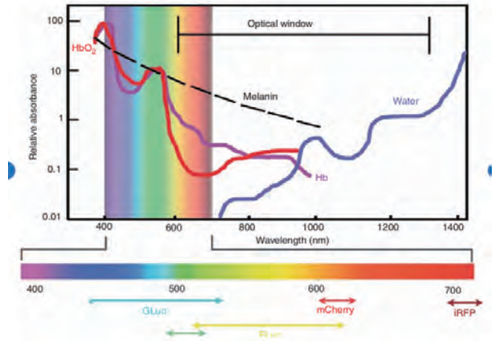


では何故、近赤外線は生体内部に進達する事が出来るのでしょうか？

人体に最も多く存在してる構成要素は水です。また、血管の長さは、極小の毛細血管まで含めると、その長さは 10 万キロメートルともいわれています。なんと、地球を 2 周半するほどの長さです。

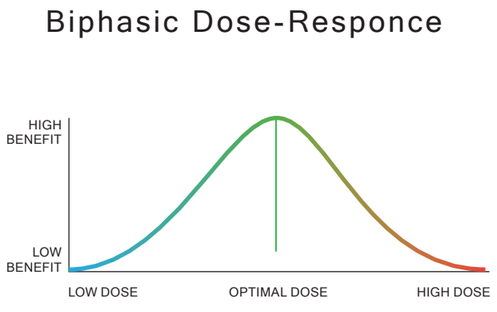
従って、光を人体に進達させようとした場合、水分と血液が光の進む道を邪魔するという事になります。

下の図は、Optical Window（光学的窓）と呼ばれるもので、ヘモグロビンと H2O が吸収される光の波長帯を示したものです。ヘモグロビンとH2O が、近赤外線の波長域では殆ど吸収されない事が分かります。従って、近赤外線が生体内部にある程度進達する事が出来るという事になります。



近赤外線を使用する上で注意すべきと言われている事

近赤外線を使用した施術には、二相性の反応が現れる事が殆どであると言われております。これは、光を当てすぎても、少なすぎても効果が低いとう意味であるとされています。従って、適切な波長を適度の強さで適当な時間照射する事が良い効果を引き出すと解釈されています。この二相性の反応には、アルント - シュルツの法則が当てはまると言われております。（これは、ホルミシス効果に似ているとも言われております。）



[アルント - シュルツの法則]

プリューゲル・アルントシュルツの刺激法則とは、刺激の強度と神経や筋の興奮性について述べた法則です。弱い刺激をすることで神経機能を喚起し、中程度の刺激で神経機能を興奮させ、強い刺激は神経機能を抑制し、最強度の刺激で静止するという法則で、つまり、適度の刺激を加えることが生体にとって最も良い刺激であると言われております。

IRの一般的な効果について（論文からの抜粋）

創傷治癒、若返り、疼痛緩和、細胞保護、細胞再生、凝りの緩和、疲労緩和、炎症の緩和、抗菌性等であると言われております。

[以下は、海外の論文から参照した、IR の効果について述べられいる内容です]

- 血管拡張効果は実証済と考えてよい
- LLLT：Low level light therapy の有益な影響は、ほぼ全ての組織と臓器が含まれる
- 膜組織・ミトコンドリアに作用し様々な回路やシグナリングを調整している
- 線維芽細胞を活性する、また、コラーゲン合成能を増大する効果がある
- 血管内皮細胞の eNOS 生産を促進する（血管が拡張され血流が良くなる）
- 光によって誘発された ROS（Reactive Oxygen Species）は短期的には光肌エイジングケアに良いが、多ければ光老化となる
- DNA の損傷に応じて DNA 修復システムを誘発する
- 抗がん剤の用量を減らせる可能性がある
- ATP 産生能を刺激する
- 脂肪幹細胞を増殖させる
- 単回投与（照射）ではなく、効果もしくは疾病の緩和が見られる迄継続的に実施する事が望ましい（食事と一緒：規則正しい食事）
- IR 放出素材は生活品質を向上させるアプリケーションである（屋外活動・睡眠・家庭介護商品であり、今後、柔軟性のあるアプリケーションとなっていくであろう）

※詳しい内容は、P14, 15 をご参照ください

IRの肌の若返り効果について（論文からの抜粋）

① 非熱光による肌の若返りに於いて、レーザーと LED は安全で効果的である。

② レーザーと LED は、ドット形状（点状）の発光特性とスペクトル帯域幅が狭いため、いくつかの欠点がある。それは、組織の再生と修復に関わるスペクトルは複数の波長で構成されるため、赤色光のみより広いスペクトル領域をカバーする波長帯がより有効であろうと考えらる事である。

③ 赤色光（IR 光を含む）は肌の若返り・皮膚内コラーゲンの増加に関し有効である。

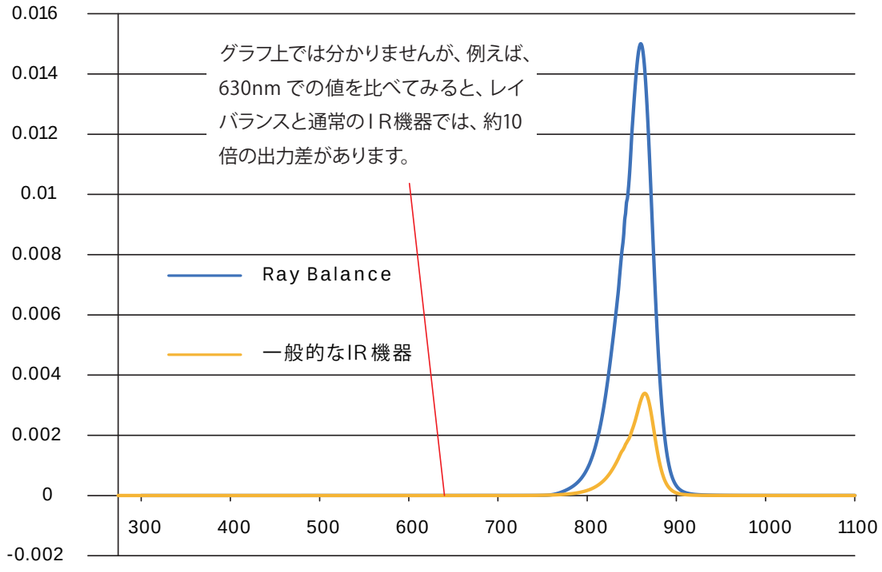
④ 600～1300nm のスペクトル範囲の光は、創傷治癒、組織修復、皮膚の若返りを促進するのに役立ちます。

⑤ LLLT および PBM で最も重要な波長は、632.8nm であり、これは、HeNe レーザーの主波長である。

⑥ アサーマル光のみの光若返りのための 590、633、および 830 nm の波長の LED 光源の使用は、近年急速に成長している。

⑦ ヒト線維芽細胞における遺伝子発現プロファイルの詳細な分析により、細胞増殖などの細胞機能に関与する 111 の異なる遺伝子に対する、波長 628 nm の低強度赤色光の影響が明らかになった。

⑧ 人間の皮膚での光誘起フリーラジカル形成が詳細に調査されており、波長 620 および 670nm の赤色光は、外部光増感剤の影響なしでも ROS の濃度を増加させることが示されている。



※詳しい内容は、P16, 17 をご参照ください

論文からの抜粋_2（創傷治癒について）

赤色および近赤外（NIR）波長領域（635、730、810、980 nm）の異なる波長の光によって媒介される LLLT の治癒効果として、マウスモデルに於ける部分的な厚さの皮膚擦過傷に対し照射し評価する実験が実施されました。以下がその結果です。

① 635 および 810 nm の波長は、皮膚擦過傷の治癒を促進するのに効果的である。

② 730 nm と 980 nm の波長を使用した治療では、刺激（光照射）による治癒の兆候は見られなかった。

③ 他の波長や非照射コントロールと比較して、810 nm で治療したマウスでは治癒が最大限に増強された。
：創傷面積の有意な減少（p <0.05）、コラーゲン蓄積の増大、完全な再上皮化が発生した。

④ サイトケラチン -14 の免疫蛍光染色と増殖細胞核抗原（PCNA）を調べる事によって明らかにされた、再上皮化と細胞増殖の有意な加速（PCNA）（p<0.05）は、他のグループと比較して 810 nm で明白だった。

⑤ 赤（635 nm）および NIR（810 nm）の光によって媒介される光生体調節は、創傷組織の生物学的応答が、使用する波長に依存することを示唆している。

⑥ 810 nm の有効性は以前の実験結果と一致し、635 nm の部分的な有効性と 730 および 980 nm の無効性は、LLLT に於ける、シトクロム c オキシダーゼ（ミトコンドリア発色団の候補）の吸収スペクトルによるものと考えられる。

まとめ①

・IR の効果については、信憑性のある国際的な論文が数多く発表されており、安心して使用頂けると考えております。

・RB は通常の IR 機よりも広い範囲の波長帯域をカバーしておりますので、この点に於きましても安心して使用頂けると考えております。

・前述した通り、身体に刺激を与える場合には、二相性の反応が現れる事がほとんどである事を注意する必要がありますが、RB の使用している光の強さはレーザー光線に比べるとそのフルエンスは非常に低く、レベル４の最強度で使用しても安心して使用頂けると考えております。
30 分以上同一の身体部分にプローブを触れさてのご使用には、低温火傷の可能性が発生しますので、その様な使用方法は避けて下さい。

TDD〈Transdermal drug delivery：経皮ドラッグデリバリー（経皮による薬液送達）〉について

物を振動（シェ―キング）させると、浸透や溶解のスピードが速くなるのは一般的によく知られています。実際、大学の研究室で組織染色する際もシェ―キングを行っています。

TDDについて

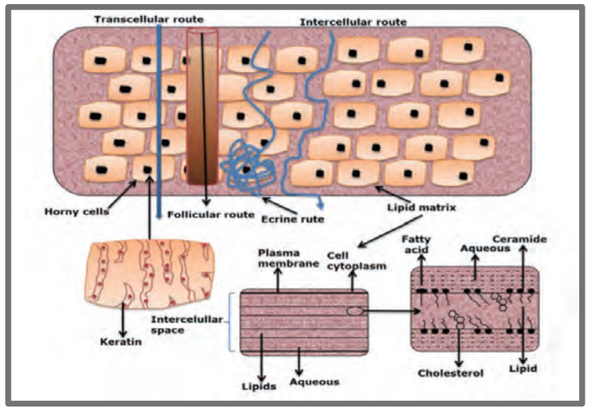
TDD（経皮ドラッグデリバリー）を考える上でまず知っておくべき事は、皮膚（角質層）はバリアであり、親水性、及び高分子の液体は基本的には通しません。従って、薬液を肌に浸透させる事を考える場合には、その薬液が親油性なのか、低分子な状態なのかを考える必要があります。

バリア（角質層）の浸透経路について

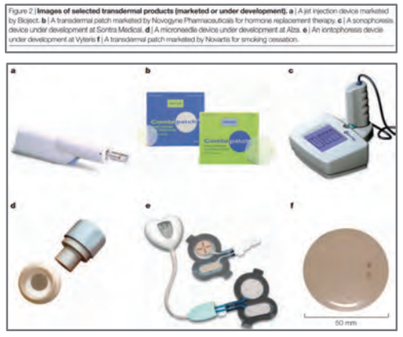
肌の最初のバリアは、角質層最外部の皮脂です。皮脂を通過して角質層の内部へ入り、その下の顆粒層へ到達する、角質層内部いある経路は以下の通りです。

- 経細胞経路（細胞実質透過経路）
- 細胞間ルート（細胞間隙経路）
- 濾胞経路（毛穴等）・・・吸収率（透過率）が最も高い
- エクリン線経路（汗腺の１つ：アポクリン線）

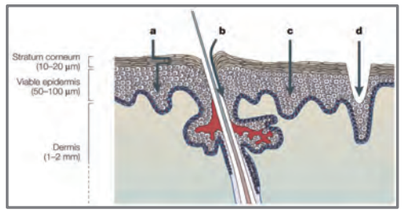
＜角質層に於ける浸透経路図 ①＞



＜TDD機器＞ 抜粋：市販製品＆開発中含む



＜角質層に於ける浸透経路図 ②＞



TDDに於いて用いられる方法について

	Passive	Active（外部の物理的トリガーを適用）							
		非熱ベース					熱ベース		非・熱双方
方法名	パッチ（粘着性経皮デリバリーシステム）	粘着テープ or 接着剤（ストリッピングン）	圧力駆動型ジェット	イオン導入（IP：イオンフォレイシス）	エレクトロポレーション	マイクロニードル	超音波（ソノフォレイシス）	熱支援マイクロポレーション（レーザー）	etc.
作用機序	受動的経皮薬物送達	角質細胞と細胞外脂質の両方が除去され、薬剤が通過する必要がある経路の長さが短縮	約100～200 m/s にて薬液を吹付け角質層に穴を開けます	電気浸透と呼ばれる：肌に電流を流し、溶質分子に電荷をかける：電荷の反発力に基づく：薬物分子に直接作用させる	脂質二重膜の習慣的な構造摂動：角質層に一時的な水性細孔を形成する：肌に作用して浸透力を高める	薬剤が塗布されたミクロサイズの小さな針を肌に挿入	マイクロバブルを生成によるキャビテーション効果と熱効果により、角質層に微視的欠陥を作成する	レーザーにより角質層に微細孔を作成する	ナノ材料を使用した光熱増強（プラズモン共鳴）、高周波（100KHz 以上）、光応答型マイクロニードル、浸透促進剤、マイクロエマルジョン、ベシクル、ナノ粒子・電子線照射、化学的エレクトロポレーション、化学的超音波、イオン導入×超音波、エレクトロポレーション×イオン導入エレクトロポレーション、非キャビテーション超音波、熱切除、マイクロダーマブレージョン（研磨）
使用範囲	ニコチンパッチ等は広く普及	最も古い物理的方法	臨床医学にて導入	いくつかの薬物に於いて成功（送達速度は電流量に比例）	加速的に使用が広がった（μs の高電圧パルスの印加）	低分子・高分子治療	局所麻酔の前処理等広く活用されている	高分子治療	
薬剤の範囲	低分子、親油性（ナノ粒子を除く）	低分子 高分子	人成長ホルモン、ソマトロピン等に使用	低分子	親油性、サイズが異なる分子	低分子 高分子	低分子、+マイクロニードル併用	低分子 高分子	
欠点	一部の薬剤のみの適応。肌荒れの可能性がある	制御と再現性の欠如。痛みや炎症の誘発	人成長ホルモン、ソマトロピン等に使用	定量送達の欠如、たんぱく質の損傷、一定の値を超えると痛みを伴う	皮膚の透過性が一瞬で元に戻る（使用しにくい）	生体的合成、皮膚の損傷	身体に対するダメージを発生させる可能性がる	火傷	

※詳しい内容は、P18 をご参照ください

振動が身体に与える影響について

[一般論]

振動が身体（頸部より下）に与える影響については、血行促進や疲労の改善がよく知られており、マッサージ器はこの最たるものです。但し、近赤外線のご説明資料に記載させて頂いた二相性の反応（アルント - シュルツの法則）が、身体に対する振動にも当てはまると言われております。これは、弱い刺激をすることで神経機能を喚起し、中程度の刺激で神経機能を興奮させ、強い刺激は神経機能を抑制し、最強度の刺激で静止するという法則で、適度の刺激を加えることが生体にとって最も良い刺激であると言われております。振動に於いても、適度な振動（強度・施術時間・施術間隔等）が肝要と言われております。

[最新の論文内容のご報告]

① **[内　容]** 生体内微小循環モードにおける皮膚血流への振動の影響
[結　論] 直接的な皮膚の振動が皮膚の血流を改善する。
（本実験に於いては、5 分後に血流増加。15 分後に減衰となった。）

② **[内　容]** 健康な人間における皮膚の血流と、その根底にある制御メカニズムに対する低強度の振動の影響の調査。
[結　論] 低強度の振動は、筋起源の血管制御メカニズムによって部分的に媒介される皮膚血流の急激な増加をもたらした。

③ **[内　容]** 健康な人間における皮膚の血流と、その根底にある制御メカニズムに対する低強度の振動の影響の調査。
[結　論] 局所間断振動は、糖尿病患者の足の皮膚血流を効果的に改善する可能性があるが、局所連続振動は同レベルの血管拡張を得ない可能性がある。糖尿病の被験者は、健康な被験者よりも、印加された振動に対する皮膚血流応答が低い。

④ **[内　容]** 全身振動が皮膚血流と一酸化窒素産生に及ぼす影響
[結　果] 低周波、低振幅の WBV は、SBF を大幅に増加させた（P = .0115）。
全血の NO 濃度については、有意差が得られなかった（P = .1813）。
[結　論] 糖尿病患者に於いて、全身振動による皮膚血流の増加がみられた。全身振動は、糖尿病の神経血管合併症の潜在的な非薬物療法になりえる可能性がある。
※ WBV：Whole Body Vibration
※ ＳＢＦ：Skin Blood Flow

⑤ **[内　容]** マウスと人間の脳機能に対する全身振動の有益な効果
[結　果] 全身振動は運動能力を改善し、マウスの覚醒誘発活動を減少させた。人間の認知テストでは、選択的な改善を得た。全身振動による刺激（介入）は、脳機能の少なくともいくつかの側面を改善できる安全な刺激（介入）である。

※詳しい内容は、P19 をご参照ください

振動が脳に与える影響について

[一般論]

頭に直接振動を与えるのは良い事ではありません。脳への影響を考える前に、ある程度年齢がいかれた方や、高血糖の傾向で血管が脆くなっている人に繰り返し行うと、潜在的に硬膜化血腫を起こす可能性があると言われております。では、どの程度の振動が危険な可能性となるのでしょうか？

[最新の論文チェックの結果]

以下、MILITARY MEDICINE という医学誌に、2020 年に発表された論文の内容を紹介します。
この論文が結論として掲載している結論は、以下の通りです。
TBI（外傷性脳障害：外傷性脳挫傷）に続く短期的な振動の影響を評価するこの研究では、中程度の振動と緊急避難に於ける空中医療をシミュレートした低酸素症が TBI 後の短期的な結果（症状）に影響を与えない。
⇒ TBI 後でも多少は安全だから健常体であれば、ある程度の振動までは問題無いと想定する事が出来ます。
※ TBI：Traumatic Brain Injury

[ご参考資料：原文より抜粋]

＜発表者＞
"Andrew D Jung, MD*; Mackenzie C Morris, MD*; Rosalie Veile, BS*; Lou Ann Friend, RVT*; Sabre Stevens-Topie, RVT§; Daniel D. Cox, et al.

"□ ABSTRACT
＜Introduction＞
Traumatic brain injury (TBI) has become increasingly prevalent among the injuries sustained in the military. Manywounded warriors require emergency medical evacuation via helicopter and subsequently fixed wing transport. Duringaeromedical evacuation, both pilots and patients experience whole body vibration due to engine, rotor, and propellerrotation. The impact of posttraumatic vibration and hypoxia exposure characteristic of the aeromedical evacuationenvironment on TBI is currently unknown.
＜Materials and Methods＞
A swine TBI model of controlled cortical impact was utilized. The pigs first underwent TBI or sham injury and weresubsequently exposed to vibration or no vibration and hypoxia or normoxia for 2 hours. They were monitored for an additional 4 hours following vibration/hypoxia and blood was drawn at hourly intervals for cytokine and serum biomarker analysis. Continuous physiologic and neurologic monitoring were utilized. Prior to the conclusion of the experiment, the animals underwent brain magnetic resonance imaging. At the end of the study, the brain was extracted for histologic analysis.
＜Results＞
Physiologic parameters except for peripheral capillary oxygen saturation (SpO2) were similar between all groups. The hypoxia groups demonstrated the expected decrease in SpO2 and pO2 during the hypoxic period, and this was sustained throughout the study period. The pH, pCO2 and electrolytes were similar among all groups. Neuron specific enolase was increased over time in the TBI group, however it was similar to the sham TBI group at all time points. There were no differences in IL-1β, IL-6, IL-8, TNFα, GFAP, HIF1α, syndecan-1, or S100β serum levels between groups. The mean ICP during cortical impact in the TBI group was 279.8 ± 56.3 mmHg. However, the postinjury ICP was not different between groups at any subsequent time point. Brain tissue oxygenation and perfusion were similar between all groups.
＜Conclusions＞
In this novel study evaluating the effect of vibration on short-term outcomes following TBI, we demonstrate that the moderate vibration and hypoxia simulating aeromedical evacuation do not impact short term outcomes following TBI."

各機能に於ける推奨強度

Vibrationを当てる身体部位	推奨強度			
	Vib 1	Vib 2	Vib 3	間断
頭部				無
頸部				無
首より下				有・無

LEDを当てる身体部位	推奨強度			
	LED 1	LED 2	LED 3	LED 4
頭部				
頸部				
首より下				

IRが治療で用いられている疾患事例

[一般的な適応例]

- 肩関節痛、腰痛、膝関節痛
- 頭痛・三叉神経痛
- 頚椎症
- 慢性関節リウマチ
- スポーツ障害
- リハビリテーション（小児を含む）
- あざ・しみ
- 歯科・口腔外科・領域
- 末梢性神経麻痺
- 新鮮帯状疱疹
- アレルギー性鼻炎

[ペインクリニックでの適応例]

- 帯状疱疹後神経痛
- 術後疼痛
- 腰痛変性すべり症
- 腰部・下肢・臀部
- 頭痛
- 頸部痛
- 肩痛
- 上肢・肘痛

まとめ②

・バイブレーターの使用に関しては、その強度に注意してご使用下さい。

MEMO

<Various medical applications of IR radiation for different cells and tissue tissues.1>

Medical application	Author, reference, et al	Year	Target	IR	Results
Wound healing	Toyokawa	2003	Skin wound in rat	Mid	Promoted wound healing and expression of TGF-β1
Wound healing	Gupta	2014	Dermal abrasions in mice	Near	Enhanced collagen accumulation and healing effects
Wound healing	Santana-Blank	2000, 2013	Soft tissues in rat	Near	Promotes wound healing and exclusion zone (EZ) growth (1H NMR 1/T2)
Wound healing	Santana-Blank Rodríguez-Santana	2013 2003	Soft tissues in rat	Near	Promotes wound healing, membrane effect measured by 1H NMR tau©
Neural stimulation	Wells	2005	Rat sciatic nerve	Mid	Generated a spatially selective response in small fascicles of the sciatic nerve
Neural stimulation	Jenkins	2013	Adult rabbit heart	Near	Induced optical pacing of the adult rabbit heart
Neural stimulation	Izzo	2006	Gerbils auditory nerve	Near	Optical radiation stimulated the cochlear response amplitudes
Neural stimulation	Duke	2012	Rat sciatic nerve	Near	Hybrid electro-optical stimulation generated sustained muscle contractions and reduced the laser power requirements
Neural stimulation	Shapiro	2012	HEK-293T cells	Near	Altered the membrane electrical capacitance during optical stimulation transiently
Photoaging	Darvin	2006	Human skin	Near	Formed free radicals and decreased content of β–carotene antioxidants
Photoaging	Schroeder	2008	Human dermal fibroblasts	Near	Increased expression of MMP-1 in the dermis
Antitumor action	Tsai	2016	HeLa cervical cancer cell	Mid	Caused a collapse of mitochondrial membrane potential and an increase in oxidative stress.
Antitumor action	Chang	2013	Breast cancer cells and normal breast epithelial cells.	Mid	Induced G2/M cancer cell cycle arrest, remodeled the microtubule network and altered the actin filament formation
Antitumor action	Tanaka	2012	A549 lung adenocarcinoma cells	Near	Activated the DNA damage response pathway
Antitumor action	Yamashita	2010	A431 (vulva), A549 (lung), HSC3 (tongue), MCF7 (breast) and Sa3 (gingiva) cancer cells	Mid	Suppressed the proliferation of cancer cells through enhancing the expression of ATF3 gene
Antitumor action	Santana-Blank	2002	Solid tumor Clinical trial	Near	88% anticancer effect. Ten years follow up
Antitumor action	Santana-Blank	2002	Solid tumor cytomorphology	Near	Selective apoptosis, necrosis, anoikis in tumor tissues of cancer patients
Antitumor action	Santana-Blank	2013	Solid tumor T2wMRI-Microdensitometry	Near	Evidence of interfacial water exclusion zone (EZ) as a predicator of anti-tumor response in cancer patients
Antitumor action	Santana-Blank	1992	Solid tumor serum levels of cytokines of peripheral leucocyte subsets	Near	Immuno-modulation in cancer patients of TNF-α sIL-2R and CD4 + CD45RA+ and CD25+ activated
Brain neural r egeneration	Naeser	2014	Mild traumatic brain injury	Near	Improved cognitive function, sleep and post-traumatic stress disorder symptoms
Brain neural r egeneration	Lapchak	2010	Strokes in embolized rabbits	Near	Increased cortical ATP content
Adipose regeneration	Wang, Y.,	2016	human adipose-derived stem cells	Near	Stimulate the proliferation and differentiation

<Various medical applications of IR radiation for different cells and tissue tissues.2> **<IR=LLLT(Razor)>**

Author, reference, et al	Year	Target	Results
Lubert	1992	Fibroblasts	Prevent cell apoptosis and improve cell proliferation, migration and adhesion
Yu	1994	Fibroblasts	Prevent cell apoptosis and improve cell proliferation, migration and adhesion
Yu	1997	Skin wound	Prevent cell apoptosis and improve cell proliferation, migration and adhesion
Grossman	1998	Keratinocytes	Prevent cell apoptosis and improve cell proliferation, migration and adhesion
Moore	2005	Endothelial cells	Prevent cell apoptosis and improve cell proliferation, migration and adhesion
Agaiby	2000	Lymphocytes	Prevent cell apoptosis and improve cell proliferation, migration and adhesion
Crysler	2003	Human gingival fibroblasts	Prevent cell apoptosis and improve cell proliferation, migration and adhesion
Gavish:	2006	Porcine aortic smooth muscle cells	Modulated matrix metalloproteinase activity and gene expression
Shefer		Muscle satellite cells	Activate muscle satellite cells, enhancing their proliferation, inhibiting differentiation and regulating protein synthesis
Hopkins	2004	Angiogenesis	Enhance neovascularisation, promote angiogenesis and increase collagen synthesis to promote healing of acute
Corazza	2007	Wound rats	Acceleration of cutaneous wound heaing with a biphasic dose response
Gigo	2004	Nerves	Stimulate healing
Results	2005	Tendons	Stimulate healing
Morrone	2000	Cartilage	Stimulate healing
Weber	2006	Bones	Stimulate healing
Shao	2005	Internal organs	Stimulate healing
Bjodal	2006	Pain, inflammation by injuries	Reduce
Carati	2003	Swelling	Reduce
Oron	2001	Injury or ischemia in skeletal and heart muscles	Beneficial（multiple animal models：in vivo）
Lapchak	2008	Damage after strokes	Mitigate damage in both animals and humans
Oron	2007	After traumatic brain injury	Mitigate damage in both animals and humans
Wu	2009	After spinal cord injury	Mitigate damage in both animals and humans

[ご参考資料：参照した論文]

Year	Author	Tittle	Abstract
2014	"Alexander Wunsch1 and Karsten Matuschka2 Author information Copyright and License information Disclaimer"	"A Controlled Trial to Determine the Efficacy of Red and Near-Infrared Light Treatment in Patient Satisfaction, Reduction of Fine Lines, Wrinkles, Skin Roughness, and Intradermal Collagen Density Increase"	**Objective:** The purpose of this study was to investigate the safety and efficacy of two novel light sources for large area and full body application, providing polychromatic, non-thermal photobiomodulation (PBM) for improving skin feeling and appearance. Background data: For nonthermal photorejuvenation, laser and LED light sources have been demonstrated to be safe and effective. However, lasers and LEDs may offer some disadvantages because of dot-shaped (punctiform) emission characteristics and their narrow spectral bandwidths. Because the action spectra for tissue regeneration and repair consist of more than one wavelength, we investigated if it is favorable to apply a polychromatic spectrum covering a broader spectral region for skin rejuvenation and repair. **Materials and methods:** A total of 136 volunteers participated in this prospective, randomized, and controlled study. Of these volunteers, 113 subjects randomly assigned into four treatment groups were treated twice a week with either 611–650 or 570–850 nm polychromatic light (normalized to ~9 J/cm2 in the range of 611–650 nm) and were compared with controls (n=23). Irradiances and treatment durations varied in all treatment groups. The data collected at baseline and after 30 sessions included blinded evaluations of clinical photography, ultrasonographic collagen density measurements, computerized digital profilometry, and an assessment of patient satisfaction. Results: The treated subjects experienced significantly improved skin complexion and skin feeling, profilometrically assessed skin roughness, and ultrasonographically measured collagen density. The blinded clinical evaluation of photographs confirmed significant improvement in the intervention groups compared with the control.Conclusions: Broadband polychromatic PBM showed no advantage over the red-light-only spectrum. However, both novel light sources that have not been previously used for PBM have demonstrated efficacy and safety for skin rejuvenation and intradermal collagen increase when compared with controls.
2009	"Asheesh Gupta, Tianhong Dai, Michael R. Hamblin"	""Effect of red and near infrared wavelengths on low-level laser (light) therapy induced healing of partial-thickness dermal abrasion in mice"	Low-level laser (light) therapy (LLLT) promotes wound healing, reduce pain, inflammation, and prevent tissue death. Studies have explored the effects of various radiant exposures on the effect of LLLT, however studies of wavelength dependency in in vivo models are less common. In the present study, healing effects of LLLT mediated by different wavelengths of light in the red and near infrared (NIR) wavelength region (635, 730, 810 and 980 nm) delivered at constant fluence (4 J/cm2) and fluence rate (10 mW/cm2) were evaluated in a mouse model of partial-thickness dermal abrasion. 635 and 810 nm wavelengths were found to be effective in promoting healing of dermal abrasions.However, treatment using 730 and 980 nm wavelengths showed no sign of stimulated healing. Healing was maximally augmented in mice treated with 810 nm as evidenced by a significant wound area reduction ($p < 0.05$), enhanced collagen accumulation, and complete re-epithelialization as compared to other wavelengths and non-illuminated controls.A significant acceleration of re-epithelialization and cellular proliferation revealed by immunofluorescence staining for cytokeratin-14 and proliferating cell nuclear antigen (PCNA) ($p < 0.05$) was evident in 810 nm compared with other groups.Photobiomodulation mediated by red (635 nm) and NIR (810nm) light suggests that the biological response of the wound tissue depends on the wavelength employed. The effectiveness of 810 nm agrees with previous publications, and together with the partial effectiveness of 635 nm and ineffectiveness of 730 and 980 nm can be explained by the absorption spectrum of cytochrome c oxidase, the candidate mitochondrial chromophore in LLLT.

2009	Barolet D., Roberge C.J., Auger F.A., Boucher A., and Germain L.	Regulation of skin collagen metabolism in vitro using a pulsed 660 nm LED light source : clinical correlation with a single-blinded study
2009	Huang Y.Y., Chen A.C.H., Carroll J.D., and Hamblin M.R.	Biphasic dose response in low level lightherapy
2007	Calderhead R.G.	The photobiological basics behind light-emitting diode (LED) phototherapy
2003	Papadavid E., and Katsambas A	Lasers for facial rejuvenation
2008	Khoury J.G., and Goldman M.P.	Use of light-emitting diode photomodulation to reduce erythema and discomfort after intense pulsed light treatment of photodamage
2005	Smith K.C.	"Laser (and LED) therapy is phototherapy"
1992	van Breugel H.H., and Bär P.R	Power density and exposure time of He-Ne laser irradiation are more important than total energy dose in photo-biomodulation of human fibroblasts in vitro
2008	Shoshani D., Markovitz E., Monsterey S.J., and Narins D.J.	The Modified Fitzpatrick Wrinkle Scale: A clinical validated measurement tool for nasolabial wrinkle severity assessment
2005	Vinck E.M., Cagnie B.J., Cornelissen M.J., Declercq H.A., and Cambier D.C.	Green light emitting diode irradiation enhances fibroblast growth impaired by high glucose level
2010	Karu T.I.	Multiple roles of cytochrome c oxidase in mammalian cells under action of red and IR-A radiation
2005	Weiss R.A., McDaniel D.H., Geronemus R.G., and Weiss M.A.	Clinical trial of a novel non-thermal LED array for reversal of photoaging: clinical, histologic, and surface profilometric results
2005	Russell B.A., Kellett N., and Reilly L.R.	A study to determine the efficacy of combination LED light therapy (633 nm and 830 nm) in facial skin rejuvenation
2008	Sadick N.S.	A study to determine the efficacy of a novel handheld light-emitting diode device in the treatment of photoaged skin
2007	Lee S.Y., Park K.H., Choi J.W., et al.	A prospective, randomized, placebo-controlled, double-blinded, and split-face clinical study on LED phototherapy for skin rejuvenation: Clinical, profilometric, histologic, ultrastructural, and biochemical evaluations and comparison of three different treatment settings
2012	Santana–Blank L., Rodríguez–Santana E., and Santana–Rodríguez K.E.	Photobiomodulation of aqueous interfaces as selective rechargeable bio-batteries in complex diseases
2008	Calderhead R.G., Kubota J., Trelles M.A., and Ohshiro T.	One mechanism behind LED phototherapy for wound healing and skin rejuvenation: Key role of the mast cell
2003	Zhang Y., Song S., Fong C.C., et al.	cDNA microarray analysis of gene expression profiles in human fibroblast cells irradiated with red light
2013	Jang Y.H., Koo G.B., Kim J.Y., Kim Y.S., and Kim Y.C.	Prolonged activation of ERK contributes to the photorejuvenation effect in photodynamic therapy in human dermal fibroblasts
2009	Zastrow L., Groth N., Klein F., et al.	The missing link–light-induced (280–1,600 nm) free radical formation in human skin.
2012	Crisan D., Crisan M., Moldovan M., Lupsor M., and Badea R.	Ultrasonographic assessment of the cutaneous changes induced by topical flavonoid therapy.
1998	Webb C., Dyson M., and Lewis W.H.	Stimulatory effect of 660 nm low level laser energy on hypertrophic scar-derived fibroblasts: possible mechanisms for increase in cell counts.
2007	Baez F., and Reilly L.R.	The use of light-emitting diode therapy in the treatment of photoaged skin.
2003	Vinck E.M., Cagnie B.J., Cornelissen M.J., Declercq H.A., and Cambier D.C.	Increased fibroblast proliferation induced by light emitting diode and low power laser irradiation.
2006	Goldberg D.J., Amin S., Russell B.A., Phelps R., Kellett N., and Reilly L.A.	Combined 633-nm and 830-nm led treatment of photoaging skin.
2010	Giacomoni P.U., Mammone T., and Teri M.	Gender-linked differences in human skin.
2011	Oh J.H., Kim Y.K., Jung J.Y., et al.	Intrinsic aging- and photoaging-dependent level changes of glycosaminoglycans and their correlation with water content in human skin.
2009	David Alan Arnall, Arnold G. Nelson, Laura Stambaugh, Nuria Sanz Sevilla, M. Angels Cebria i Iranzo, et al,	Pulsed infrared light therapy does not increase nitric oxide concentration in the blood of patients with type 1 and type 2 diabetes mellitus
2006	David Alan Arnall, Arnold G. Nelson, Nuria Sanz Sevilla, Laura Lo´pez Bueno	The restorative effects of pulsed infrared light therapy on significant loss of peripheral protective sensation in patients with long-term type 1 and type 2 diabetes mellitus
2002	Alan B Kochman, Dale H Carnegie, Thomas J. Burke	Symptomatic Reversal of Peripheral Neuropathy in Patients with Diabetes
2012	Chung H., Dai T., Sharma S., Huang Y.Y., Carroll J., and Hamblin M.	The nuts and bolts of low-level laser (light) therapy
1981	.Anderson R.R., and Parrish J.A.	The optics of human skin
1998	Gupta A.K., Filonenko N., Salansky N., and Sauder D.N.	The use of low energy photon therapy (LEPT) in venous leg ulcers: a double-blind, placebo-controlled study
2009	Minatel D.G., Frade M.A., Franca S.C., and Enwemeka C.S.	Phototherapy promotes healing of chronic diabetic leg ulcers that failed to respond to other therapies

[ご参考資料：参照した論文]

Year	Author	Tittle	Abstract
2018	Sabine Szunerits* and imageRabah Boukherroub	Heat: A Highly Efficient Skin Enhancer for Transdermal Drug Delivery	Transdermal delivery systems have become a successful alternative for a continuous drug delivery on demand. The clinical potential of light-based transdermal activation using lasers, photodiodes and in combination with light-to-heat converting materials is large. Considering the progress made in the transdermal field, the future of transdermal drug delivery depends largely on the implementation of novel approaches to overcome constraints of passive diffusion without compromising skin integrity.
2012	Amit Alexander, Shubhangi Dwivedi, Ajazuddin, Tapan K. Giri, Swarnlata Saraf Shailendra Saraf, Dulal Krishna Tripathi	"Approaches for breaking the barriers of drug permeation through transdermal drug delivery"	Transdermal drug delivery system (TDDS) utilizes the skin as executable route for drug administration but the foremost barrier against drug permeability is the stratum corneum and therefore, it limits therapeutic bioavailability of the bioactive. This review focuses on the recent advancements in the TDDS which include iontophoresis, sonophoresis, electroporation, microneedles, magnetophoresis, photomechanical waves and electron beam irradiation. These advancements are exhaustively discussed with techniques involved with their beneficial claims for different categories of bioactive. However, a lot of research has been carried out in TDDS, still the system has many pros and cons such as inconsistent drug release, prevention of burst release formulation and problems related to toxicity. In addition to that, to exploit the TDDS more efficiently scientists have worked on some combinational approaches for manufacturing TDDS viz., chemical–iontophoresis, chemical–electroporation, chemical–ultrasound, iontophoresis–ultrasound, electroporation–iontophoresis electroporation–ultrasound and pressure waves–chemicals and reported the synergistic effect of the same for safe, effective and practical use of TDDS. The present article covers all the above-mentioned aspects in detail and hence the article will assuredly serve as an enlightening tool for the visionaries working in the concerned area.
2014	Mark R. Prausnitz*, Samir Mitragotri and Robert Langer	"CURRENT STATUS AND FUTURE POTENTIAL OF TRANSDERMAL DRUG DELIVERY"	The development of transdermal delivery systems involves balancing increased transdermal transport with patient safety/comfort and cost. Because intact skin is not sufficiently permeable to the large majority of drugs, enhancement methods are needed. Despite extensive research during the past few decades, hemical enhancers have achieved only limited success in increasing transdermal transport of small molecules and have only a relatively poor ability to increase macromolecular transport under conditions likely to be clinically acceptable. Methods involving ultrasound and electric fields, including iontophoresis and electroporation, have more extensively increased transdermal delivery for small drugs and macromolecules. The ability of these technologies to deliver drugs effectively is partially counterbalanced by their reliance on electronically controlled devices that require an energy source, which constrains applications and cost. Methods that pierce micron-scale holes in skin, such as microneedles, thermal poration and jet injection, can dramatically increase transdermal delivery of small drugs, macromolecules and even particles, butmore work is needed to establish safety/skin damage and cost effectiveness. Each of these technologies is likely to suit the needs of different applications and, in some cases, combinations of enhancers might be the most effective strategy (TABLE 2).
2008	Mark R Prausnitz1 & Robert Langer2	Transdermal drug delivery	Overall, transdermal drug delivery offers compelling opportunities to address the low bioavailability of many oral drugs, the pain and inconvenience of injections, and the limited controlled-release options of both. Building off the successes of first-generation transdermal patches, second-generation chemical enhancers and iontophoresis are expanding delivery capabilities for small molecules, whereas third-generation physical enhancers (including ultrasound, thermal ablation and microneedles) could enable transdermal delivery of macromolecules and vaccines. These scientific and technological advances that enable targeted disruption of stratum corneum while protecting deeper tissues have brought the field to a new level of capabilities that position transdermal drug delivery for an increasingly widespread impact on medicine.
2015	Mei-Chin Chen, Ming-Hung Ling, Kuan-Wen Wang, Zhi-Wei Lin, Bo-Hung Lai, Dong-Hwang Chen	Near-infrared light-responsive composite microneedles for on-demand transdermal drug delivery	This study presents near-infrared (NIR) light-responsive polymer-nanostructure composite microneedles used for on-demand transdermal drug delivery. Silica-coated lanthanum hexaboride (LaB6@SiO2) nanostructures were incorporated into polycaprolactone microneedles, serving as an NIR absorber. When the microneedles were irradiated with NIR light, light-to-heat transduction mediated by the LaB6@SiO2 nanostructures caused the microneedle melting at 50° C. This increased the mobility of the polymer chains, enabling drug release from the matrix. Drug release from the microneedles was evaluated for four laser on/off cycles. In each cycle, the samples were irradiated until the temperature reached 50° C for 3 min (laser on); the laser was then turned off for 30 min (laser off). The results showed that light-induced phase transition in the polymer triggered drug release from the melted microneedles. A stepwise drug-release behavior was observed after multiple cycles of NIR light exposure. No notable drug leakage was found in the off state. This NIR-light-triggerable device exhibits excellent reproducibility, low off-state leakage, and noninvasive triggerability and, thus, represents an advance in transdermal delivery technology.
2004	Weiyong Li, David Nadig, Henrik T. Rasmussen, Kudan Patel, Tridarsh Shah	"Sample preparation optimization for assay of active pharmaceutical ingredients in a transdermal drug delivery system using experimental designs"	"A simple but very effective sample preparation method is discussed for a matrix or drug-in-adhesive type of transdermal drug delivery system (TDS). The method is a one-step extraction using a methanol/water solvent system. Because of the unique design and physical property of the delivery system, special considerations were taken in selection of sample solvent, sample container and extraction enhancement device. The main focus of the article is on method optimization using experimental designs. A Plackett–Burman design was used to screen multiple method factors including extraction solvent strength, extraction solvent volume, shaking speed of a reciprocating shaker, and shaking time. Later, two of the factors were studied in more details using a 4 × 5 general factorial design. From the experimental results, the so-called main effects plots and interaction plots were generated using a statistical software. The plots are helpful in choosing the method conditions."

[ご参考資料：原文の内容抜粋]

	Author	Tittle	Abstract
①	Andrew D Jung, MD*; Mackenzie C Morris, MD*; Rosalie Veile, BS*; Lou Ann Friend, RVT*; Sabre Stevens-Topie, RVT§; Daniel D. Cox, et al.	Effect of vibration on skin blood flow in an in vivo microcirculatory model	The effect of vibration on skin microcirculation was studied to investigate the possibility of clinical use of vibration to prevent and treat pressure ulcers. Vibrations at a vibrational intensity of 600, 800, or 1,000 mVpp with a fixed frequency of 47 Hz were applied horizontally to the ear of male hairless mice (n = 6 for each group) under inhalation anesthesia. The control group (n = 6) received no vibrations. Venular blood flow was measured by an intravital videomicroscope at the baseline and at 0, 5, and 15 min after the application of vibrations. A significant increase was observed in the 600 mVpp group 5 and 15 min after vibration in comparison to the control group (P = 0.002 and P = 0.046, respectively). We also detected increased blood flow in the 800 mVpp group (P = 0.028) and the 1,000 mVpp group (P = 0.012) 5 min after vibration; however, these increases attenuated after 15 min. These results indicate that direct skin vibration at a frequency of 47 Hz improves skin blood flow. The present study gives further support to the role of vibration on a short-term increase in skin blood flow.
②	"Yi-Ting Tzen1, Eileen M. Weinheimer-Haus2, Thomas F. Corbiere2, Timothy J. Koh2* et al."	"Increased skin blood flow during low intensity vibration in human participants: Analysis of control mechanisms using short-time Fourier transform"	Low intensity vibration produced acute increases in skin blood flow mediated in part by vascular control mechanisms of myogenic origin. Further investigation is warranted to determine whether low intensity vibration induces similar increases in skin blood flow in populations prone to developing chronic non-healing wounds, such as spinal cord injury and diabetes.
③	"Weiyan Ren1†, Fang Pu2,3†, Huiqin Luan1, Yijie Duan2, Honglun Su1, Yubo Fan1,2,3* and Yih-Kuen Jan3,4*, Yijie Duan2, Honglun Su1, Yubo Fan1,2,3* and Yih-Kuen Jan3,4*"	Effects of Local Vibration With Different Intermittent Durations on Skin Blood Flow Responses in Diabetic People	For diabetic subjects, the SBF was significantly increased in both Vibration and Recovery Stage with local intermittent vibrations (LIV1 and LIV2), but not with LCV. However, there was no significant difference in change percentage and change rate of SBF in diabetic subjects across the three tests. For healthy subjects, all vibration interventions significantly increased the SBF in the Vibration Stage and in the first 1.5 min of the Recovery Stage. Also, the change rate of SBF during the Vibration stage in LIV1 test was significantly greater than that in LIV2 test for healthy subjects. Moreover, change percentage of SBF in Vibration stage of LIV1 test and in some periods of Recovery stages of LIV1 and LIV2 tests for diabetic subjects were lower than for healthy subjects; the absolute change rate of SBF in LIV1 test for diabetic subjects was also lower than for healthy subjects. ※LIV：Local intermittent vibrations、LCV：Local continuous vibration
④	"Paula K. Johnson, MS1, J. Brent Feland, PT, PhD1 A. Wayne Johnson, PT, PhD1, Gary W. Mack, PhD1 and Ulrike H. Mitchell, PT, PhD1"	"Effect of Whole Body Vibration on Skin Blood Flow and Nitric Oxide Production"	"Results: Low-frequency, low-amplitude WBV significantly increased SBF compared to the sham condition (F2,18 = 5.82, P =.0115). Whole blood NO concentrations did not differ between the WBV and sham conditions immediately or 5 minutes after treatment (F2,18 = 1.88, P = .1813). Conclusions: These findings demonstrate that patients with diabetes respond to WBV with increased SBF compared to the sham condition. The implication is that WBV is a potential nonpharmacological therapy for neurovascular complications of diabetes."
⑤	"Ate S. Boerema1,2 , Marelle Heesterbeek2 , Selma A. Boersma1,2, Regien Schoemaker2, Erik F. J. de Vries1, Marieke J. G. van Heuvelen3 and Eddy A. Van der Zee2"	The Relationship of Three-Dimensional Human Skull Motion to Brain Tissue Deformation in Magnetic Resonance Elastography Studies	In summary, PET imaging revealed that glucose uptake was not changed as a consequence of a 5-week WBV intervention. The WBV did, however, improve motor performance and reduced arousal-induced activity in mice. Cognitive tests in humans revealed a selective improvement in the Stroop Color-Word test. Taken together, it is concluded that our WBV intervention is a safe intervention that can improve at least some aspects of brain functioning. A limitation of the cognitive test in the human study, however, might be that we did not control for variables such as dietary supplements, caffeine intake, or sleep quality. Other factors influencing the direct comparison between mice and humans are based on the inherent differences between the species. Mice received WBV while standing on 4 legs, sitting or lying down, or a combination of these, whereas our 2-legged human participant were seated. Also the number of WBV sessions and the duration of the WBV session (respectively, 37 and 10 minutes in mice, and 27 and 4 minutes in humans were not similar. The reason for the lower number of WBV sessions in humans was to ensure high adherence rates and to prevent to ask too much from our participants and supervisors (in case of the older participants).The shorter duration of the WBV session was based on pilot studies in which it was found that WBV sessions longer than 4 minutes were perceived as too long for the older participants as used in this study. Nonetheless, we found positive effects of WBV in both mice and humans.