

# PHOTODYNAMIC THERAPY An Update

Thomas E. Hoffman, M.D  
Adjunct Clinical Professor of Dermatology  
Stanford University  
President, PDA

## Photodynamic Therapy (PDT)

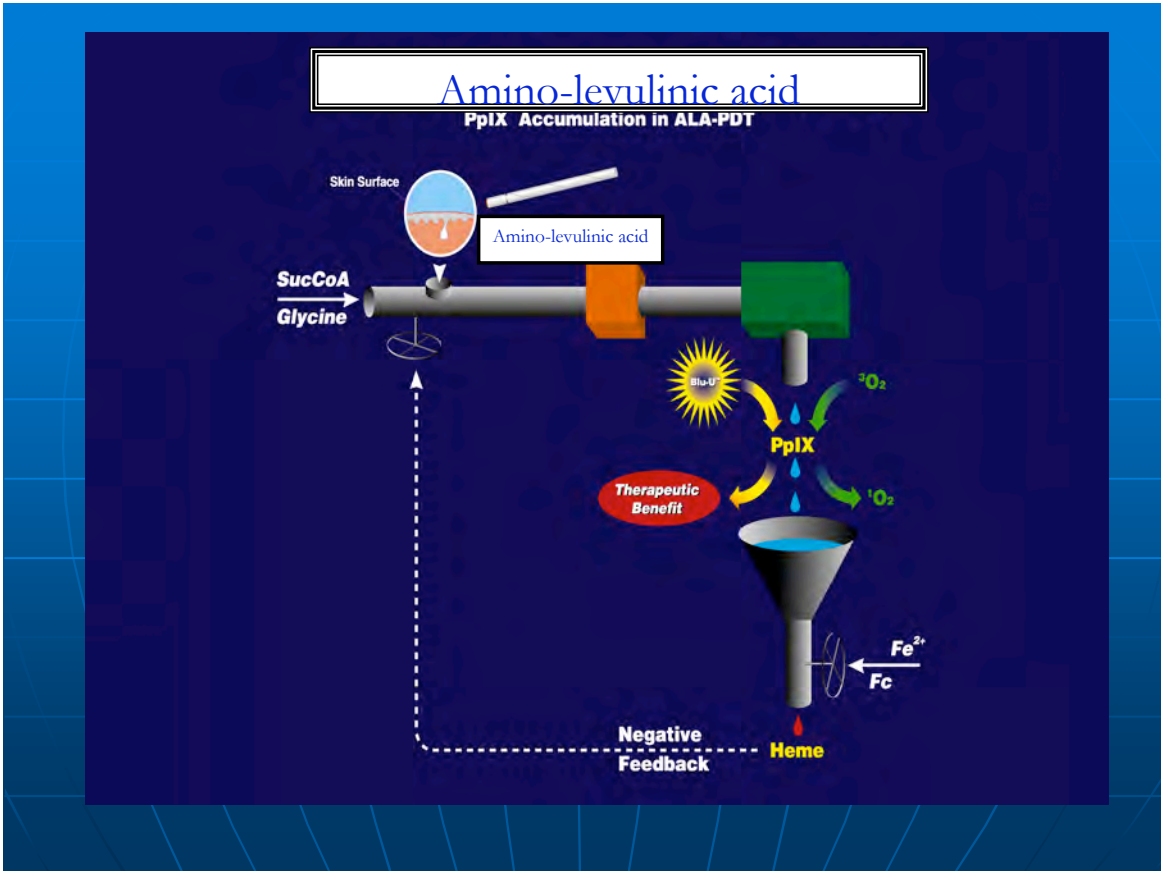
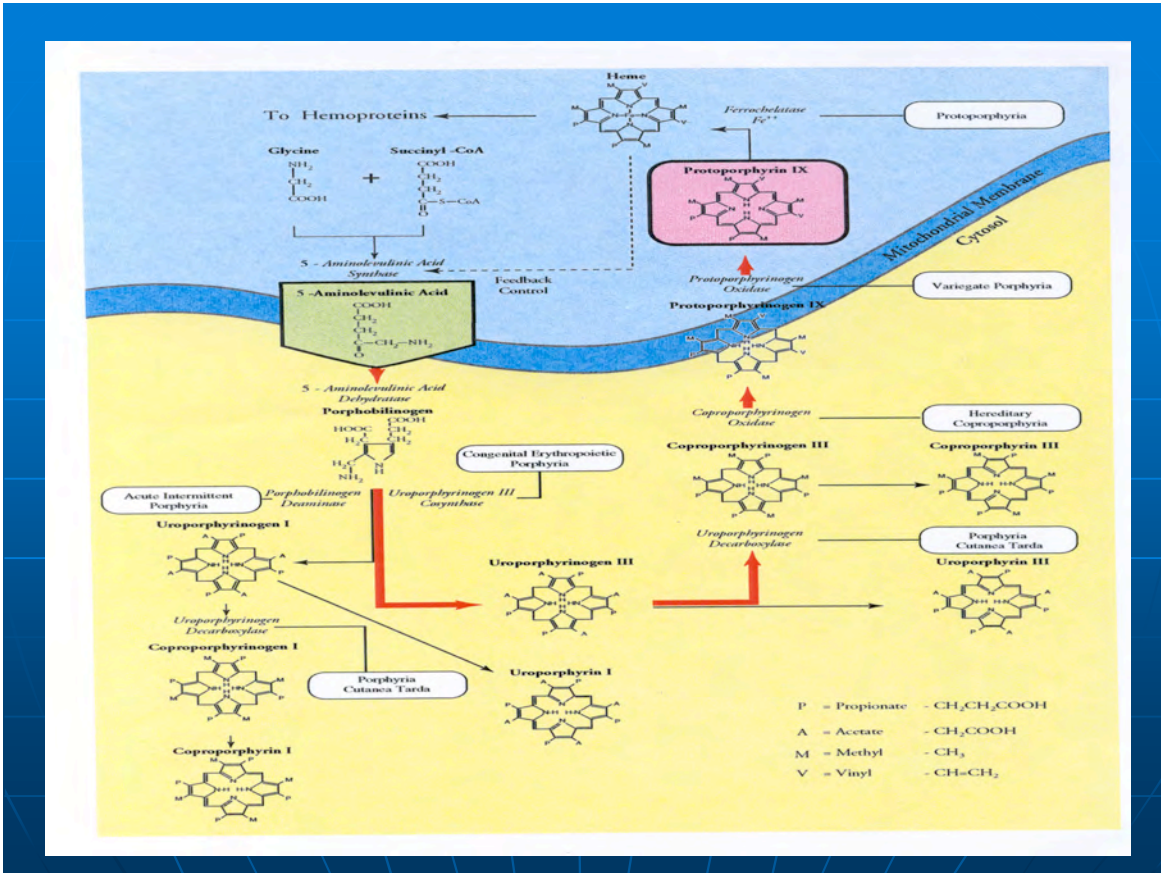
- 2 Stage Process
  - Delivery of photosensitizer (PS)
  - Photoactivation
- Oxygen an absolute requirement:
  - $O_2 + PS + \text{light} \rightarrow \text{Singlet Oxygen}$

# Evolution of PDT

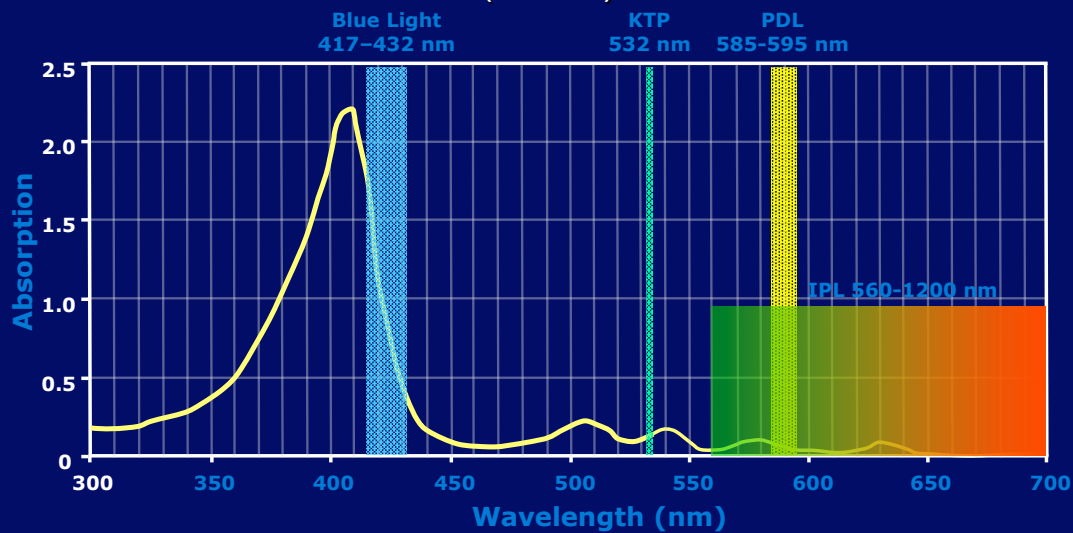
- 1. eosin red or erythrosine use with light for PR, Psoriasis, Molluscum Contagiosum, Superficial BCC in early 1900s
- 2. hematoporphyrin derivative (HPD) given systemically for primary skin cancer and cutaneous metastases in 1970s resulted in prolonged photosensativity
- 3. topical porphyrin precursors in 1990s

## ALA PDT - Using an Endogenous Photosensitizer

- **ALA (aminolevulinic acid) is taken up by cells and converted to protoporphyrin IX (PpIX), a potent photosensitizer**
- **Precancerous, malignant, or fast-growing cells identified by PpIX fluorescence**
- **Exposure to intense light of appropriate wavelength activates PpIX, leading to cell death**
- **Selective therapeutic benefit of ALA PDT is due to selective drug application followed by the accumulation of PpIX in target cells**



## PpIX Absorption Peaks (*in vivo*)

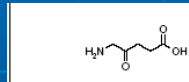


## Currently Available Porphyrin Precursors

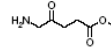
- 1. 5-aminolevulinic acid (ALA)- solution-more rapid uptake into targeted cells, higher concentration in targeted cells, hydrophilic
- 2. methyl ester of 5-aminolevulinic acid (MAL)-cream- more selective accumulation into targeted cells, may penetrate more deeply, lipophilic

# ALA and ALA Methyl Ester

- 5-aminolevulinic acid



- 5-aminolevulinic ester



## Practical Application of PDT

- 1. FDA approval for non-hypertrophic/hyperkeratotic actinic keratoses
- 2. Evolving applications: superficial bcc, Bowen's disease, thin nodular bcc, acne, photodamaged skin, verrucae, rosacea, CTCL

# TYPES OF LIGHT SOURCES

- 1. Conventional: incandescent lamps, high pressure arc lamps, low pressure arc lamps (fluorescent), light emitting diodes, flashlamp IPL
- Lasers: Diode lasers, pulse dye lasers

## Commercially Available Light Sources

- 1. Narrow band blue fluorescent tubes for ALA-PDT
- 2. Narrow band red light illumination lamp for MAL-PDT
- 3. Other light sources such as pulse dye lasers and IPL devices have been used with success reported in various publications



## ALA-PDT For Treatment Of Actinic Keratoses

- Current FDA approval for ALA-PDT involves 14—18 hour incubation with a 20% solution, for selectively treated AKs followed by activation with fluorescent blue light
- Current trend for ALA-PDT is to treat entire field of areas of AKs with short incubation time of one hour followed by light exposure (more practical and less painful)
- Current FDA approval for MAL-PDT involves applying a 16.8 % cream under occlusive dressing for 3 hours followed by illumination with a narrow spectrum red light lamp

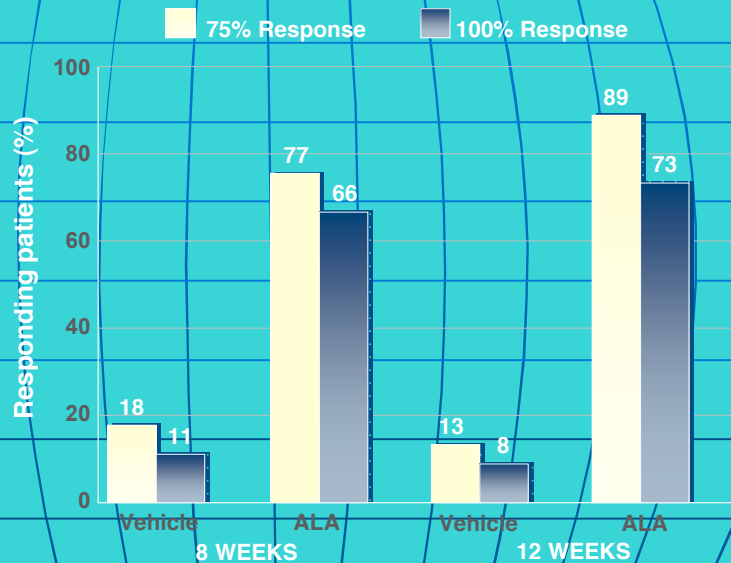
## Efficacy Of PDT for Treatment of Actinic Keratoses

- 50% to 71% complete clearance rates with one treatment in published studies
- 88% to 90% clearance rates with two or more treatments
- Face and scalp had highest clearance rates
- More efficacious compared to cryotherapy
- Quicker response and less erythema and scaling than with topical 5-FU or Imiquimod

# Literature review on PDT for treatment of AKS for ALA-PDT

- 1. Smith S, et al. Short incubation PDT versus 5-FU in treating actinic keratoses. *J Drugs Dermatol.* 2003;2 (6):629-635. -PDT better tolerated with equal or better efficacy
- 2. Touma D, et al. A trial of short incubation, broad-area photodynamic therapy for facial actinic keratoses and diffuse photodamage. *ArchDermatol.* 2004; 140:33-40-treated broad areas with 1-3 hour ALA incubation-excellent response up to 5 months with improvement of appearance of photodamage in wrinkling, sallowness, and dyspigmentation

## Phase III Study Summary: Efficacy

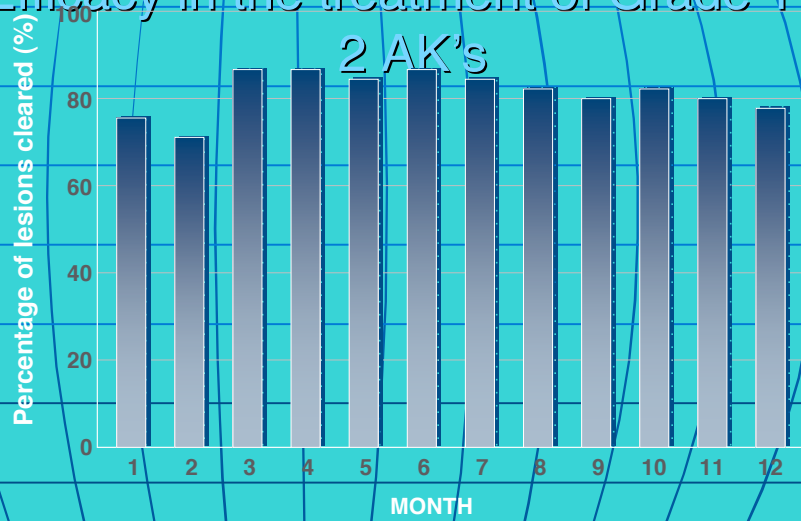


Piacquadio DJ et al. *Archives of Dermatology.* 2004;140:41-46.

MKT-1457 Rev A



# Phase IV, 110 Patient Study: Summary of Long-Term Safety & Efficacy in the treatment of Grade 1 &



Tschen EH et al. *British Journal of Dermatology*. 2006;155:1262-1269.

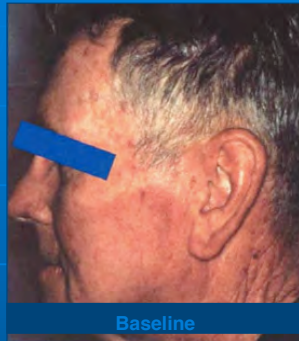
MKT-1457 Rev A

## ALA-PDT before & after spot treatment



MKT-1457 Rev A

# ALA-PDT before & after



MKT-1457 Rev A

# ALA-PDT before & after



MKT-1457 Rev A

Touma D, Yaar M, Whitehead S et al. A trial of short incubation, broad-area photodynamic therapy for facial actinic keratoses and diffuse photodamage. *Arch Dermatol* 2004; 140: 33-40.



Touma D, Yaar M, Whitehead S et al. A trial of short incubation, broad-area photodynamic therapy for facial actinic keratoses and diffuse photodamage. *Arch Dermatol* 2004; 140: 33-40.

Representative patient receiving full-face application of ALA 20% for 1 hour prior to fluorescent blue light treatment.





Touma D, Yaar M, Whitehead S et al. A trial of short incubation, broad-area photodynamic therapy for facial actinic keratoses and diffuse photodamage. *Arch Dermatol* 2004; 140: 33-40.

Representative patient receiving full-face application of ALA 20% 20% solution for 2 hours prior to fluorescent blue light treatment.



## Comparison of ALA-PDT with MAL-PDT

	<b>ALA-PDT</b>	<b>MAL-PDT</b>
<b>API</b>	Aminolevulinic acid HCl	Aminolevulinic acid methyl ester
<b>Formulation</b>	Alcohol / water solution	Oil in water cream
<b>Strength</b>	20%	16.8%
<b>proved Indications</b>	Actinic Keratosis (US)	Actinic Keratosis (US, EU) BCC (EU)
<b>AK Lesion Preparation</b>	Facial Scrub	Curettage
<b>Light Activation by</b>	Blue fluorescent light	Red Light (LED)
<b>Efficacy (% Lesion Clearance)</b>	80-90%	80-90%
<b>Safety Concerns</b>	Photosensitivity 24-48 hours s/p Tx	ACD, Photosensitivity Dermatitis
<b>Incubation Time</b>	14 - 18 hours label 1 hour recent articles	3 hours under occlusion

## Studies showing greater than 68 % clearance with MAL-PDT

- Szemies RM et al. JAAD 2002; 47:258-62
- Pariser DM et al. JAAD 2003; 48: 414-8

Better  
cosmetic outcomes  
and efficacy than  
cryotherapy

## MAL-PDT vs. ALA-PDT for AKS

- MAL was less painful than ALA in treatment of AKs using same red light source. Kasche, A et al. J Drugs Dermatol 2006; 5: 353-6

## ALA- PDT before and after 12 weeks



## ALA-PDT before and after 12 weeks



## ALA-PDT before and after 10 weeks full field short contact



## ALA-PDT before and after 10 weeks





## ALA-PDT full field short contact



2/19/2008



4/17/2008

## ALA-PDT full field short contact



2/19/2008



4/17/2008

## ALA-PDT full field short contact

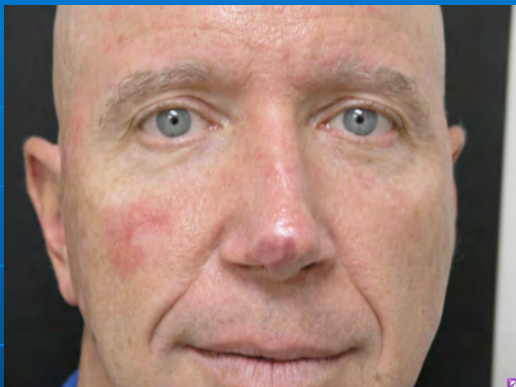


2/19/2008



4/17/2008

## ALA-PDT full field short contact



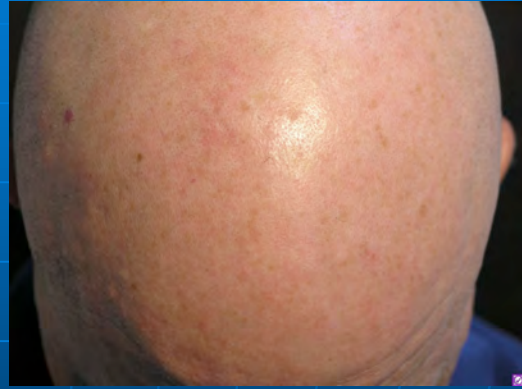
1/15/2008



3/26/2008



1/15/2008



3/26/2008



1/15/2008



3/26/2008





1/15/2008



3/26/2008

## PDT treatment for Bowen's Disease (BD) or SCC in Situ

- ALA-PDT clears , on average, 86-93% of lesions of BD following one or two treatments. Guidelines for topical PDT- Morton CA, et al. Br J Dermatol 2002: 146:552-67
- ALA treatment of BD utilizing a pulse dye laser light source was effective in 17 patients using 4 hour incubation and overlapping 7 mm diameter spots size with 82% complete clearance at 1 year. Britton JER, et al. Br J Dermatol 2005;153:780-4

# Bowen's Disease

- MAL-PDT was more effective in clearing lesions and showed a superior cosmetic effect compared to cryotherapy and topical 5-FU Morton CA, et al Arch Dermatol 2006; 142:729-35
- Various case reports have shown effectiveness of PDT to treat Bowen's Disease of the nipple, sub-ungual SCC in situ, Bowenoid papulosis, and erythroplasia of Queryat

# PDT treatment for Basal Cell Carcinoma

- A review article of 12 studies showed a weighted clearance rate of 87% for superficial basal cell carcinomas treated with ALA-PDT, but only 53% clearance for nodular bcc. Peng Q, et al. Cancer 1997;79:2282-308
- MAL-PDT with broadband light and pre-treatment curettage used to treat group of 350 superficial and nodular BCC showed an overall cure rate of 79% after 35 months with a good to excellent cosmetic response in 98%. Soler AM, et al. BR J Dermatol 2001;145:467-71

## Basal Cell Carcinoma

- ALA-PDT was compared with MAL-PDT with red light irradiance for treatment of nodular bcc. There was no difference in lesional response on histologic analysis after 8 weeks. Kuijpers D et al. J Drugs Dermatol 2006;5:642-5
- A study of 95 patients with 148 bcc lesions in "difficult to treat" sites, large size or recurrent were treated with MAL-PDT and red light. There was an 89% complete response rate at 3 months and an estimated complete response rate of 78% at 2 years. 84% were judged to have a good or excellent cosmetic response. Vinciullo C et al. Br J Dermatol 2005;152:765-72

## Basal Cell Carcinoma

- A multicenter randomized trial for treatment of nodular bcc compared MAL-PDT and red light with standard surgical excision. A similar complete response of 91% vs. 98% was noted at 3 months, but fell to 83% vs. 96% at 12 months and to 76% vs. 96% at 5 years, PDT offered a more favorable cosmetic response. Rhodes LE, et al. Arch Dermatol 2007;143:1131-6

## Basal Cell Carcinoma

- MAL-PDT compared with cryotherapy for superficial bcc showed similar complete response rates at 3 months and 5 years, but with superior cosmetic outcome for PDT. Basset-Seguin N, et al Eur J Dermatol 2008;18:547-53

## PDT for Basal Cell Nevus Syndrome

- Poster presentation at 2008 AAD meeting by Dept of Derm. Boston U. Five BCNS patients treated broadly with topical 20 % ALA solution/blue light and tumors greater than 4 mm diameter were injected intralesionally with solution diluted with lidocaine/epi resulted in clearing of most of the lesions and a reduction of new lesions seen up to 5 years follow-up



# Broad Area PDT in BCNS Patients

G.S. 67 years old



Pretreatment



After  
3 Treatments

Gilchrest et al. Derm Surgery, 2009 (in press)

# Intralesional Treatment of Nodular BCC in a Patient with BCNS



Pretreatment



1 month

BluU lamp (417 nm) 10 J/cm<sup>2</sup>

ALA 20% diluted 1:1 in 1% lidocaine

No recurrence after 4 years.

Courtesy of Barbara A. Gilchrest, M.D.

## 10-year-old boy with BCCs and Basaloid Follicular Hamartomas A) 24 hours post-PDT and B) After 2 ALA PDT Treatments



[From Oseroff, AR, Shieh, S, Frawley, NP, et al *Arch. Dermatol.* 2005; 141:60-67]

## PDT for Photorejuvenation

- Several studies done to assess treatment for AKs have shown promise for reducing the appearance of fine lines and wrinkles, photoaging, telangiectasia, and melasma

## Photorejuvenation

- ALA with blue light resulted in 83% response rate of AKs and significant reduction in crow's feet, skin roughness, hyperpigmentation, and facial erythema. Gold MH Cutis 2002;69(6 Suppl);8-13
- Split face comparison of ALA-PDT-IPL with IPL alone showed better clearing of AKS and above photodamage indicators with ALA-PDT-IPL. Gold MH, et al. Dermatol Surg 2006;32:795-801

## Photorejuvenation

- ALA-PDT one hour incubation followed by blue light cleared 90% of AKs with 72% improvement in skin texture and 59% reduction of pigmentary changes. Goldman MP, J Lasers Surg Med 2002;14(S) et al. 2002;14(S):24
- ALA-PDL more effective than PDL alone for photoaging. Key DJ. Cosmetic Dermatol 2005;18:31-36

## Photorejuvenation

- MAL-PDT with red light showed improvement in mottled hyperpigmentation, fine lines, roughness, and sallowness. Zane C, et al. Lasers Surg Med 2007;39:203-9

## PDT for Skin Cancer Prevention Organ Transplant Recipients

- MAL-PDT red light treated sites compared with control sites in renal transplant recipients with AKs showed longer time to develop new lesions in MAL treated sites and by 12 mos. 62 % of treated sites were free of new lesions compared with 35 % of control. Wulf HC. Acta Derm Venereol 2006;86:25-8

## PDT for Acne

- Most reports show better efficacy for red light or IPL over blue light irradiation
- ALA red light treated areas on the back showed a reduction of inflammatory lesions at 10 weeks with one treatment and a greater reduction after 20 week with four treatments compared to controls. Hongcharu W et al. J Invest Dermatol 2000;115:183-92

## Acne

- Very short contact ALA-blue light PDT compared with blue light alone showed moderate improvement with increased response with PDT over blue light alone. Goldman MP, Boyce. J Drugs Dermatol 2003;2:4: 393-6

## Acne

- ALA-PDT irradiated with PDL vs. PDL alone for facial acne showed a 77% lesional clearance rate for PDT treated patients vs. 32% for PDL only patients at 6 mos after a mean of 2.9 treatments. Alexiades-Armenakas M. *J Drugs Dermatol* 2006;5:45-55

## Acne

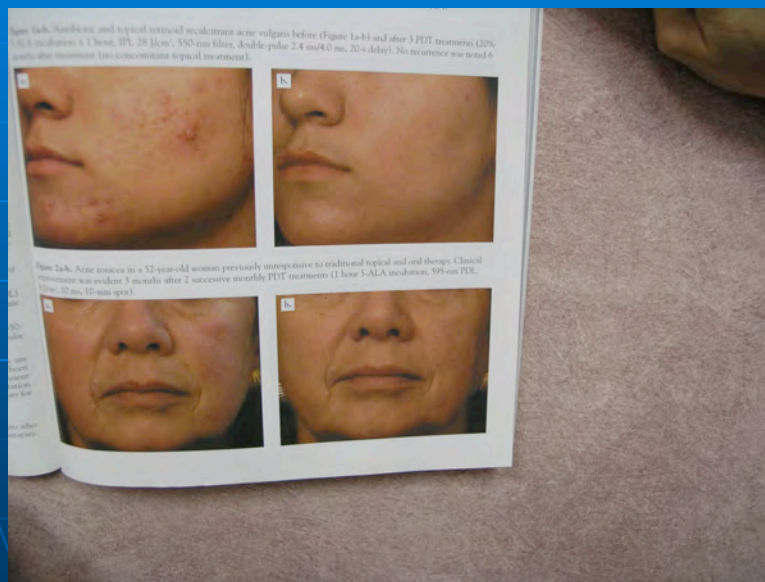
- MAL-PDT red light for two treatments vs. controls for moderate to severe facial acne showed a 69% reduction in inflammatory lesions with PDT vs. no change in the control group. Moderate pain during treatment, followed by erythema, pustules, and desquamation. Weigell SR, Wulf HC. *Br J Dermatol* 2006; 154:969-76



# ALA-PDT with blue light for acne



# ALA- PDT for Acne using IPL ALA-PDT for Rosacea using PDL





## PDT for Sebaceous Hyperplasia Papules

- Several case reports and case series report a therapeutic benefit for PDT using ALA or MAL with various light sources
- Alster TS, Tanzi EL. Photodynamic therapy with topical aminolevulinic acid and pulsed dye laser irradiation for sebaceous hyperplasia. J Drug Dermatol 2003; 2:501-4

## PDT for Viral Warts

- Clearance rates of 56-100% for PDT using ALA or MAL with various light sources have been noted in case series and comparison trials of refractory warts. Recent studies support the potential of PDT for plantar warts, but with outcomes dependent on adequate paring and the use of a keratolytic agent pre-PDT

# PDT for Cutaneous T-Cell Lymphoma

- Several case reports and case series successfully utilizing ALA-PDT and MAL-PDT for early stage localized CTCL have been published. While topical PDT can elicit a response further studies are needed to define optimal treatment parameters

## Other applications for PDT based on case reports and small case series

- Actinic cheilitis
- DSAP
- Extramammary Paget's
- Rosacea/Perioral dermatitis
- HaileyHailey
- Darriers
- NLD
- Molluscum contagiosum
- Flegel's disease
- Toenail onychomycosis
- Hidradenitis suppurativa
- ALA,MAL,red,broad
- ALA,MAL,red,PDL
- ALA,MAL,red
- ALA,MAL,red,blue, PDL
- ALA,red
- ALA,red,blue
- MAL,red
- ALA,blue
- ALA,red
- Urea occlusion, ALA,red-PDL
- ALA.blue

# Summary of applications for PDT

- Excellent for ALA or MAL for treating thin to moderate AKS, Bowen's Disease, Superficial BCC, and photorejuvenation with any light source
- Good emerging evidence for ALA or MAL for thin nodular BCC with red light
- Good emerging evidence for ALA or MAL for treatment of warts and skin cancer prophylaxis in OTR recipients
- Fair emerging evidence for ALA or MAL for acne, rosacea, extramammary Paget's, and CTCL
- Many other condition reported to be affected by PDT in case reports need further confirmation.