

**IARC Night Shift Work Carcinogenicity Classification
Workshop: Experimental Animal and Mechanistic Studies
Occupational Cancer Research Centre
Toronto Canada – 2/14/2012**



**NIGHT SHIFT
WORK/LIGHT AT
NIGHT**



BROKEN TIMING

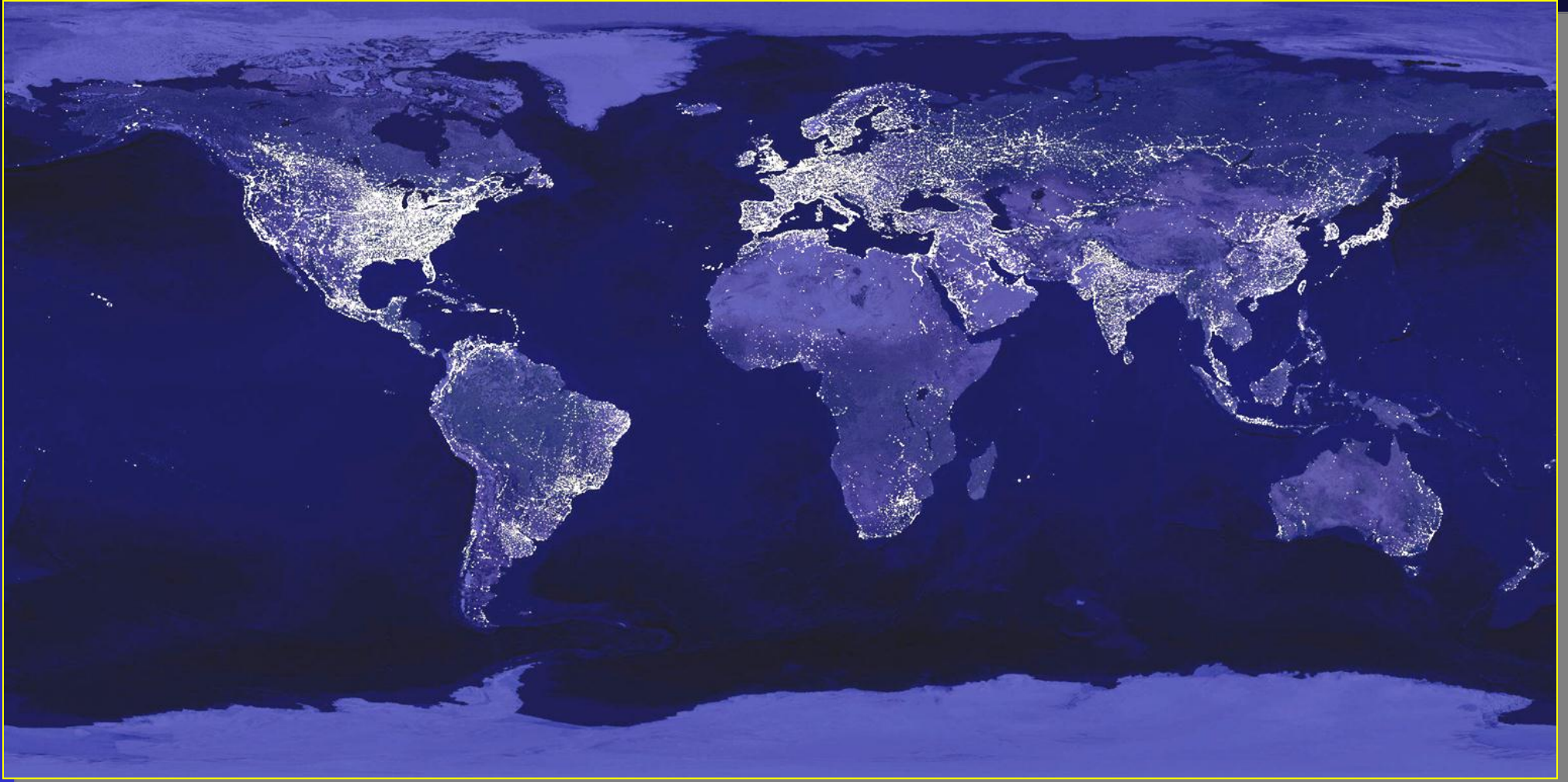


CANCER

**David E. Blask, PhD, MD
Laboratory of Chrono-Neuroendocrine Oncology
Department of Structural & Cellular Biology
Tulane University School of Medicine**

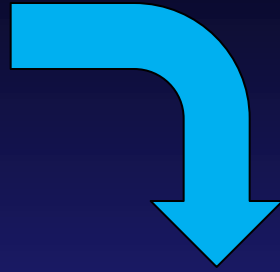


Light At Night Worldwide

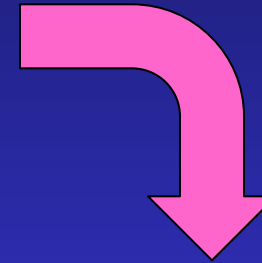




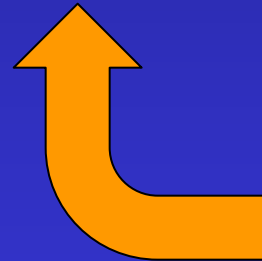
LIGHT AT NIGHT

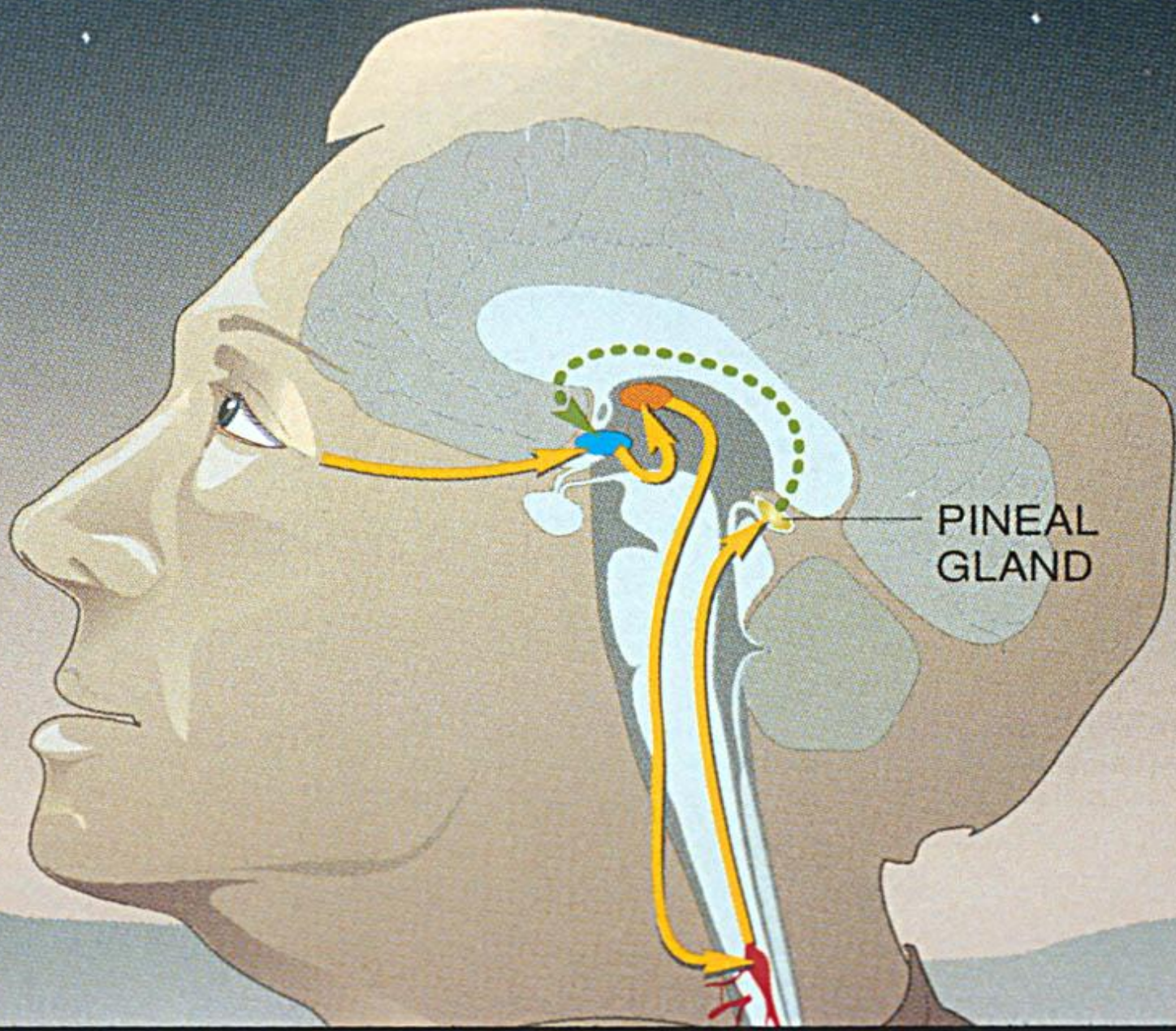


BROKEN TIMING



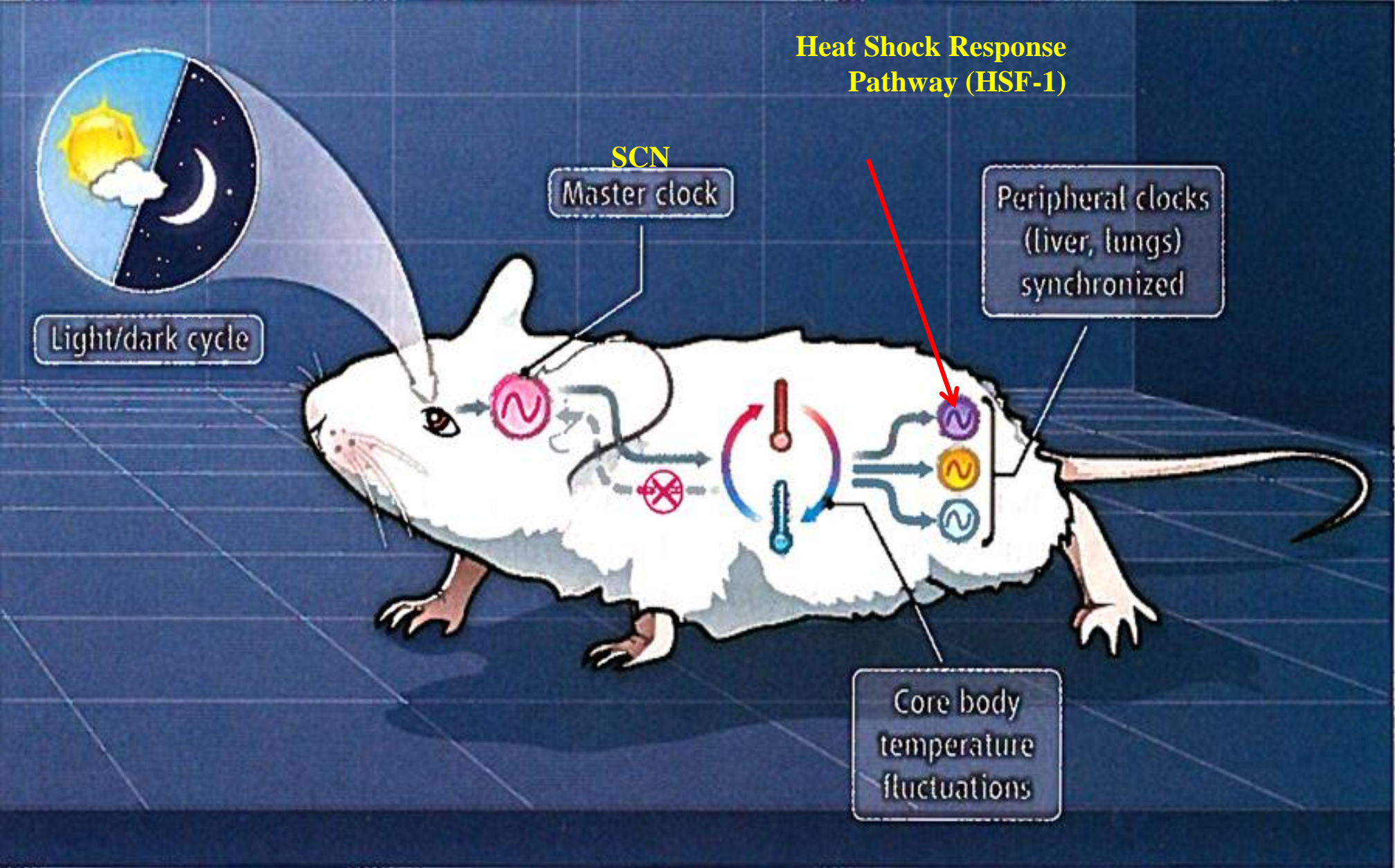
CANCER



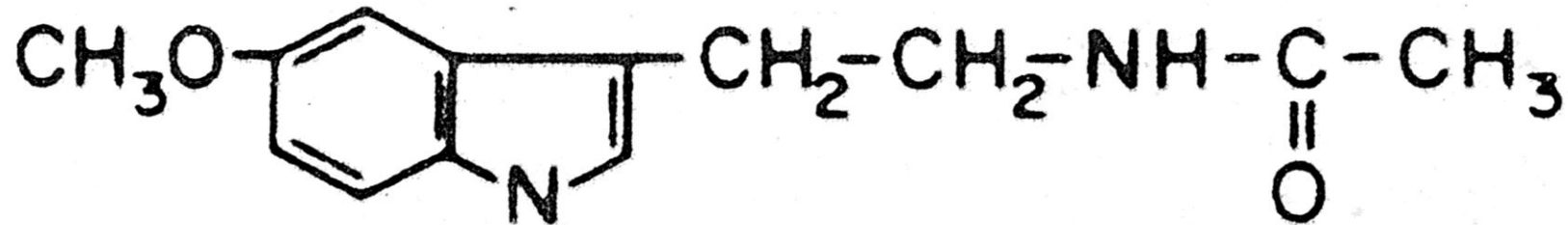


PINEAL
GLAND

Core Body Temperature Rhythm Entrain Peripheral Circadian Clocks



MELATONIN'S CHEMICAL STRUCTURE



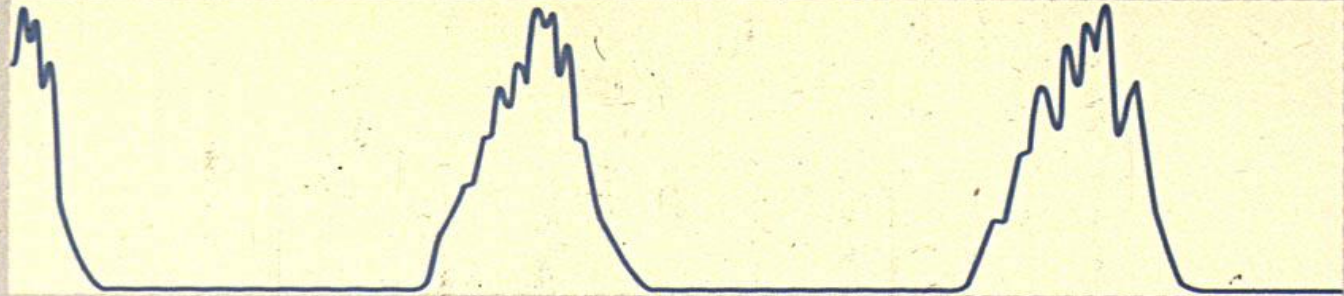
N-acetyl-5-methoxytryptamine (Melatonin)

CIRCADIAN RHYTHMS

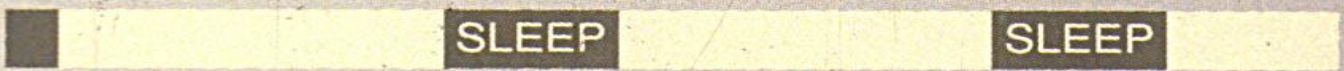
ENVIRONMENTAL
LIGHT
INTENSITY



PLASMA
MELATONIN
CONCENTRATION



SLEEP-WAKE
CYCLE



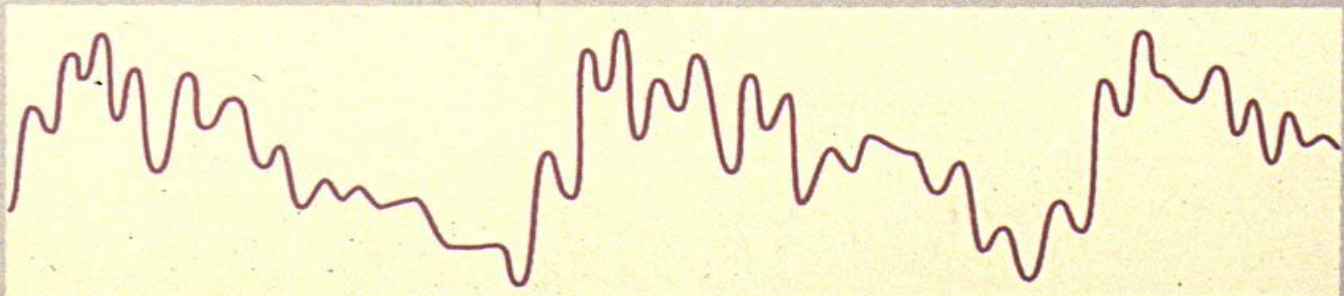
TIME OF DAY

8 16 24 8 16 24 8

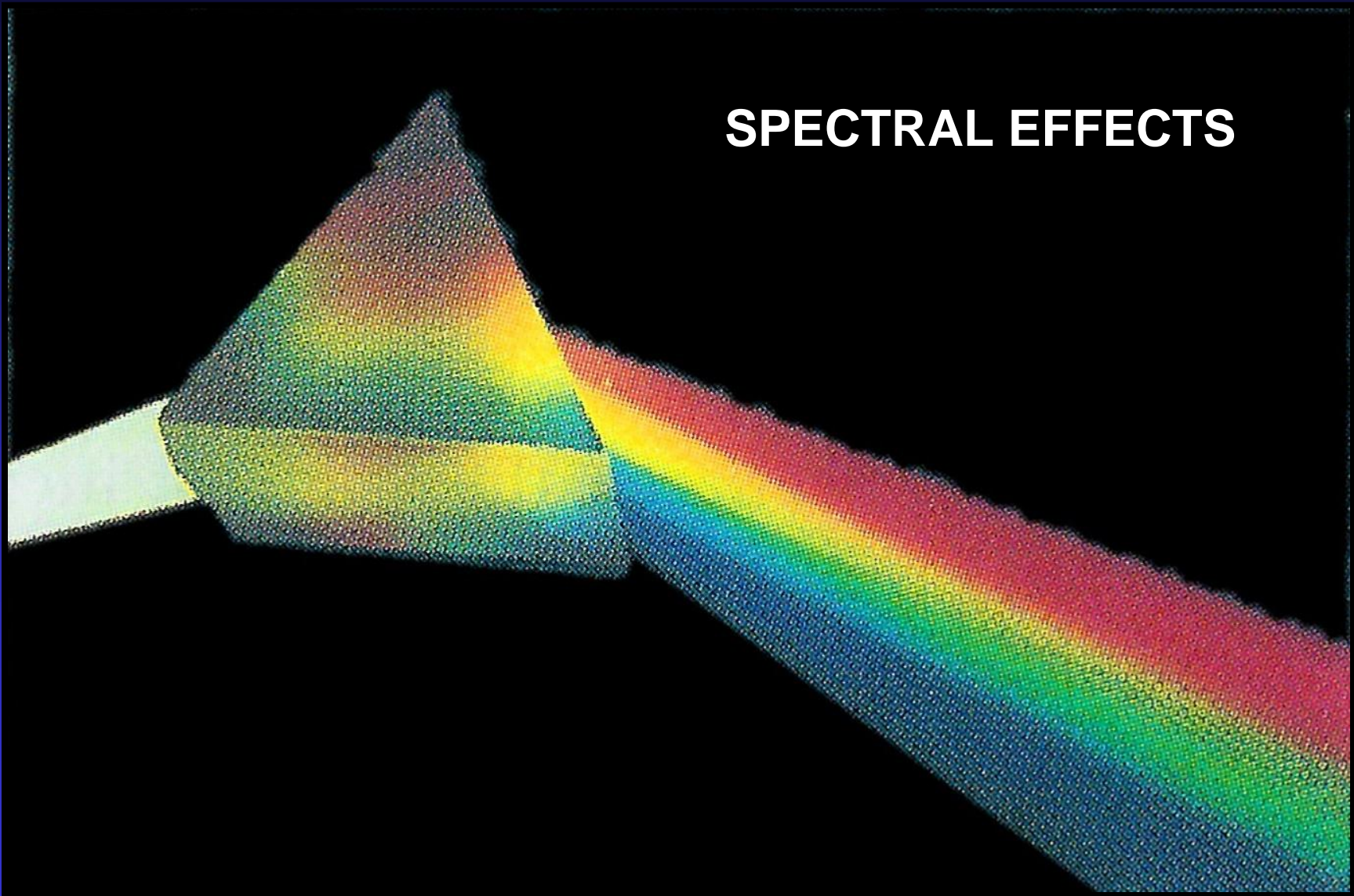
BODY
TEMPERATURE

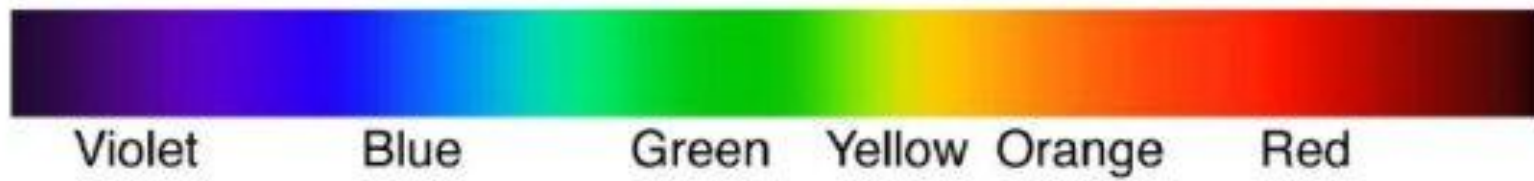
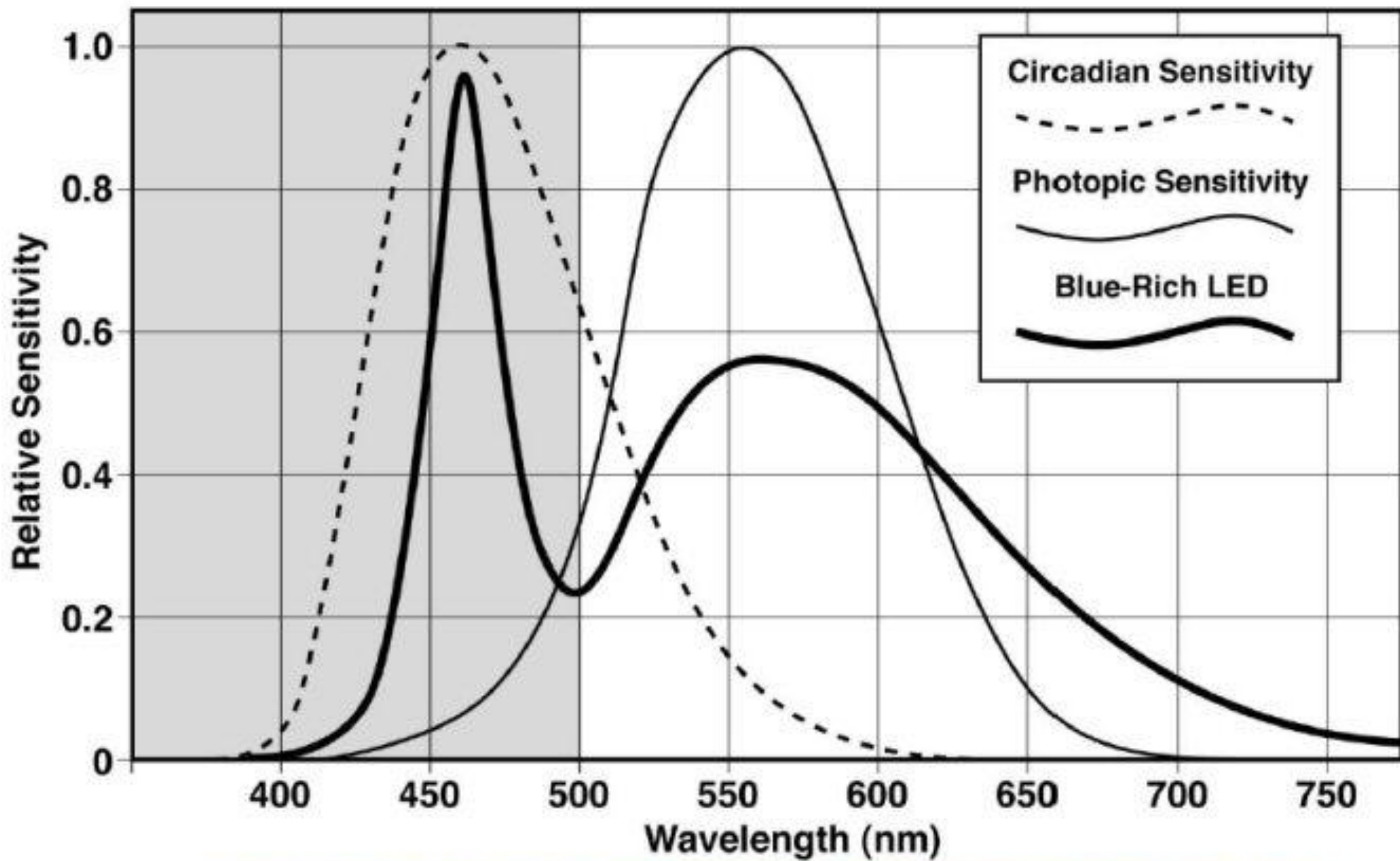


PLASMA
CORTISOL
CONCENTRATION

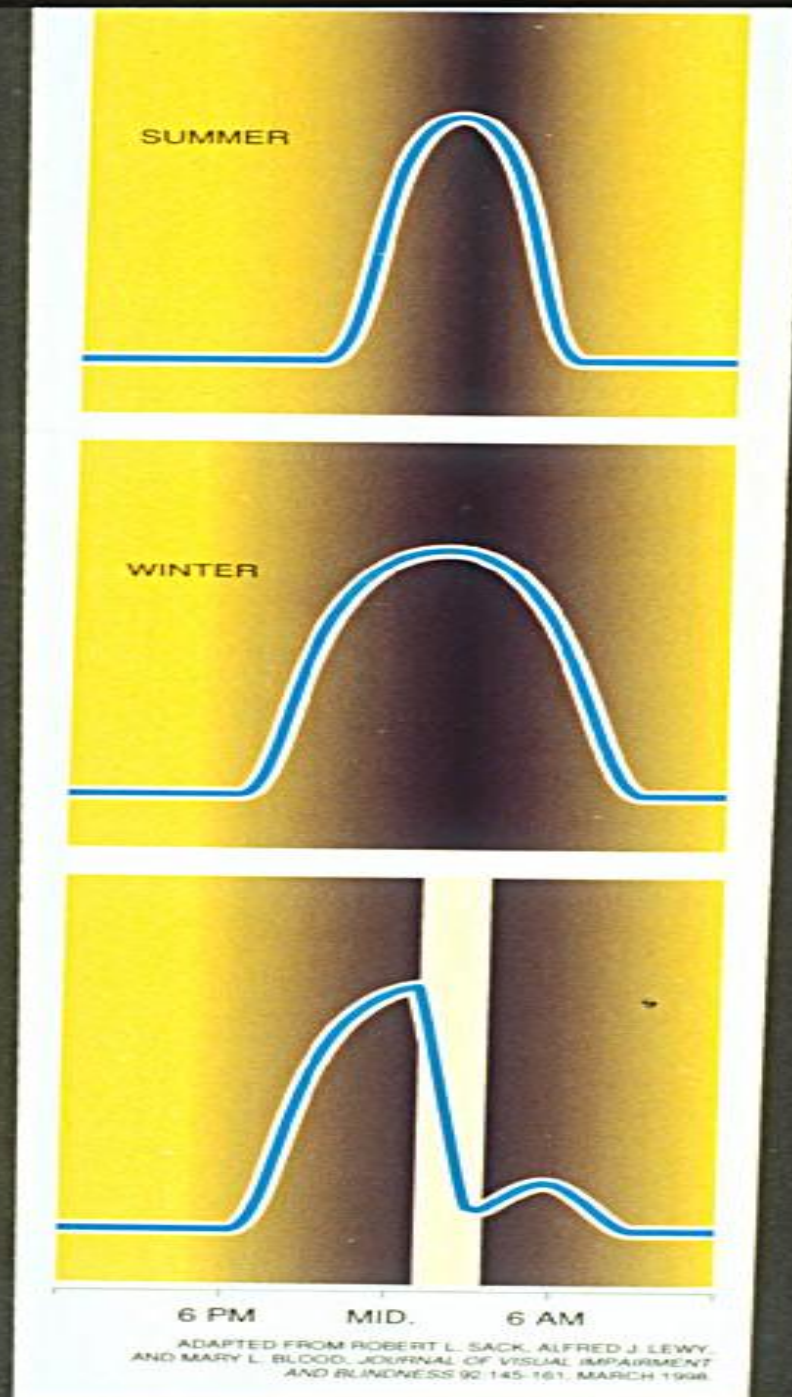


SPECTRAL EFFECTS





**IMPACT OF
PHOTOPERIODIC
DAYLENGTH ON THE
DURATION OF THE
NOCTURNAL
MELATONIN SIGNAL**



Types of Circadian Disruption Induced by Light

- **Change in Rhythm Phase (e.g., delay or advance)**
- **Change in Rhythm Amplitude (e.g, melatonin suppression by LAN)**
- **Change in Rhythm Duration (e.g., “short night”)**

Consequences of Exposure to LAN

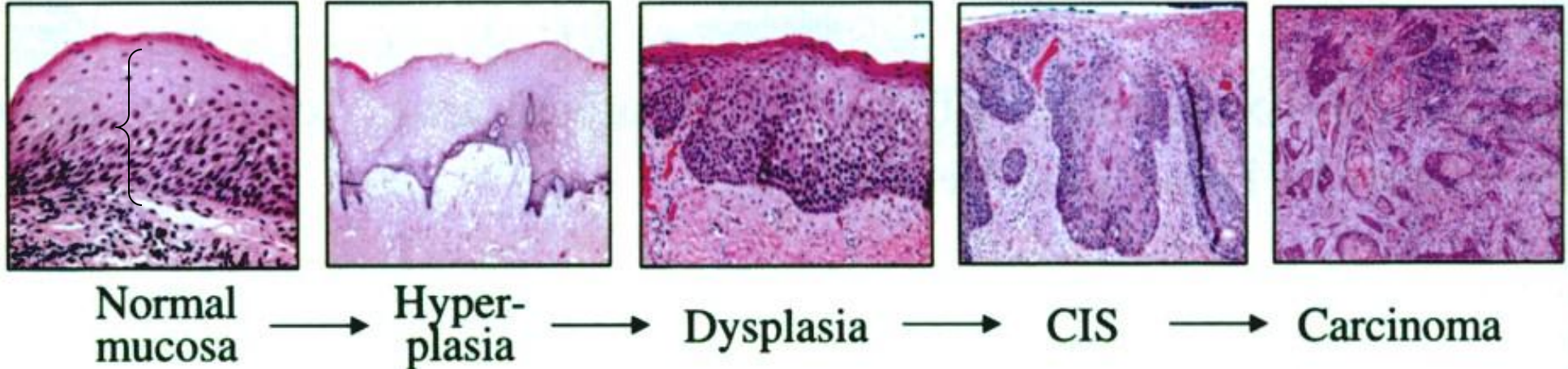
- **Disrupts circadian gene function in the SCN that impacts cell-cycle regulation and DNA repair**
- **Impact of LAN on SCN may be modified by genetic variants of circadian core clock genes (e.g., Per 3)**
- **May provide possible mechanism for putative carcinogenic effect of LAN involving melatonin suppression or not**

Studies on Cancer in Experimental Animals

	No other exposure	Chemical Initiation / promotion	Tumour cell transplantation	Total
Alterations in light exposures*	2 / 3	5 / 6	10 / 10	17 / 19
Experimental jet-lag (chronic)	-	-	2 / 2	2 / 2
SCN lesions	-	-	1 / 1	1 / 1
Pinealectomy	-	2 / 8	11 / 13	13 / 21
Physiological concentrations of melatonin	-	-	5 / 5	5 / 5
Clock gene mutations	1 / 1	1 / 2	-	2 / 3
Total	3 / 4	8 / 16	29 / 31	40 / 51

* Continuous bright light at night, dim light at night, intermittent or pulsed light at night

CARCINOGENESIS: DEVELOPMENT, GROWTH AND SPREAD OF CANCER



Initiation → Promotion/Progression → Invasion/Metastasis

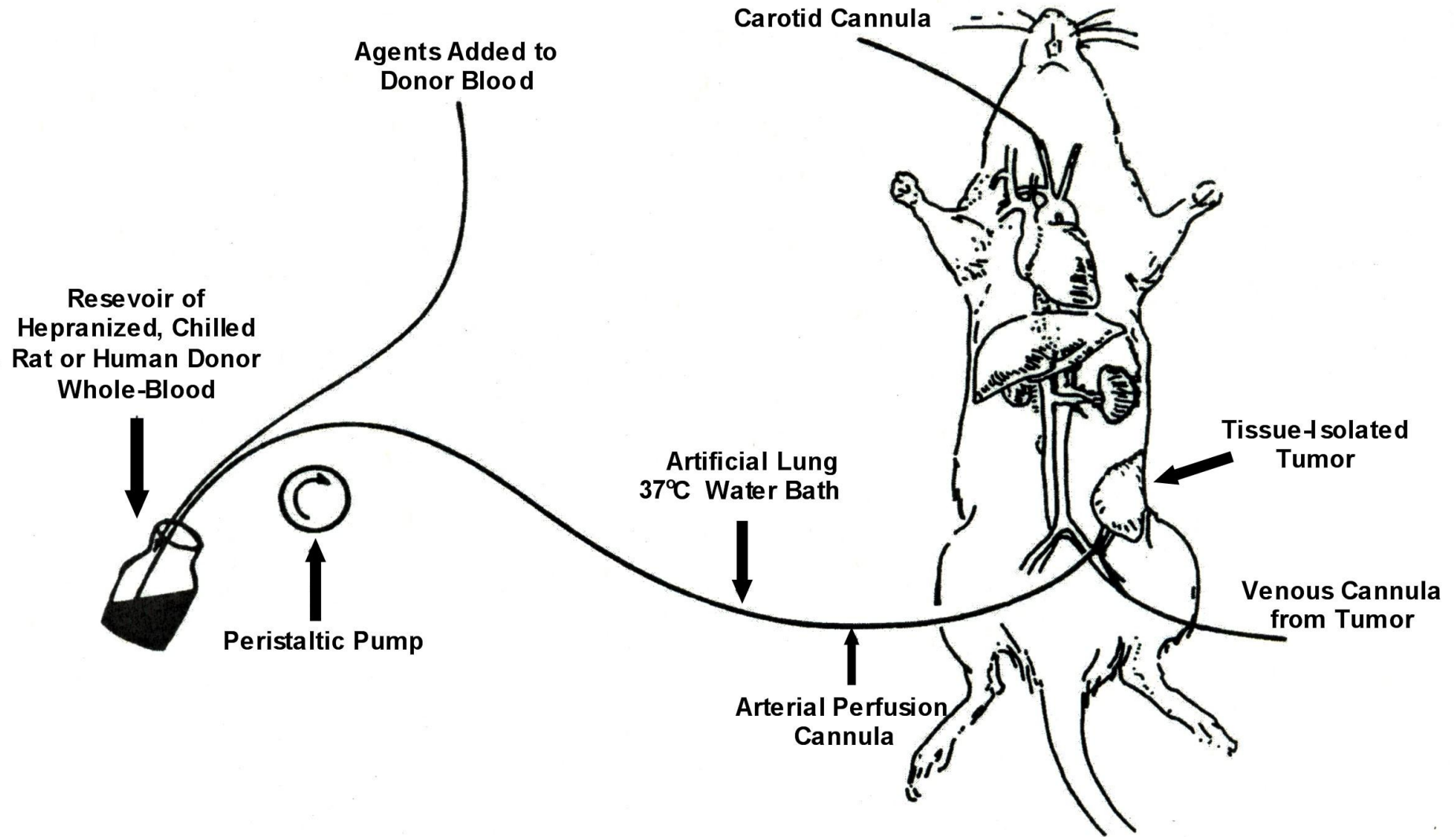
MELATONIN (+ or -)

Initiation (DNA Damage/Repair), Differentiation, Proliferation/
Survival (Apoptosis), Signal Transduction, Metabolism,
Invasion/Metastasis

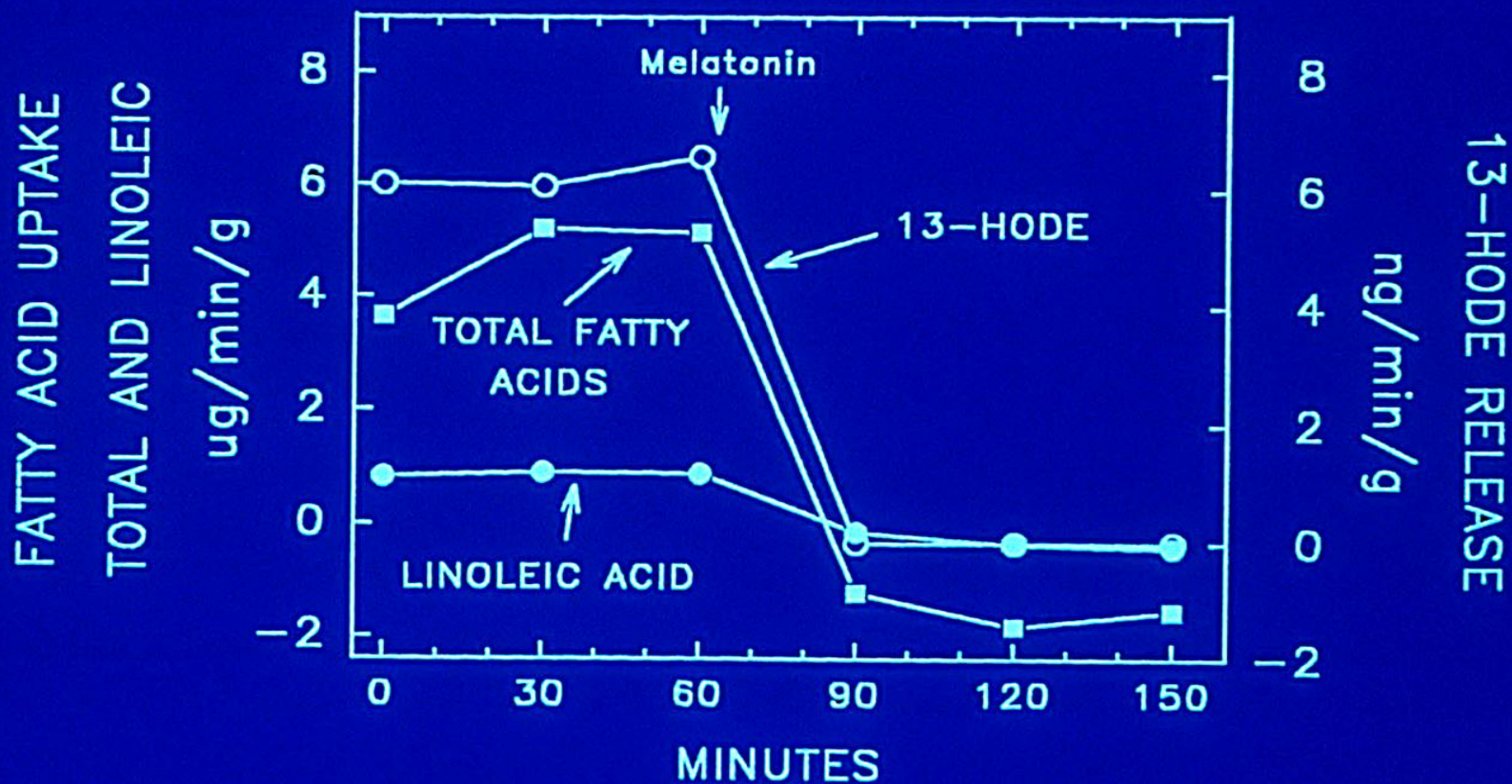
Proposed Mechanisms of Melatonin's Oncostatic Effects

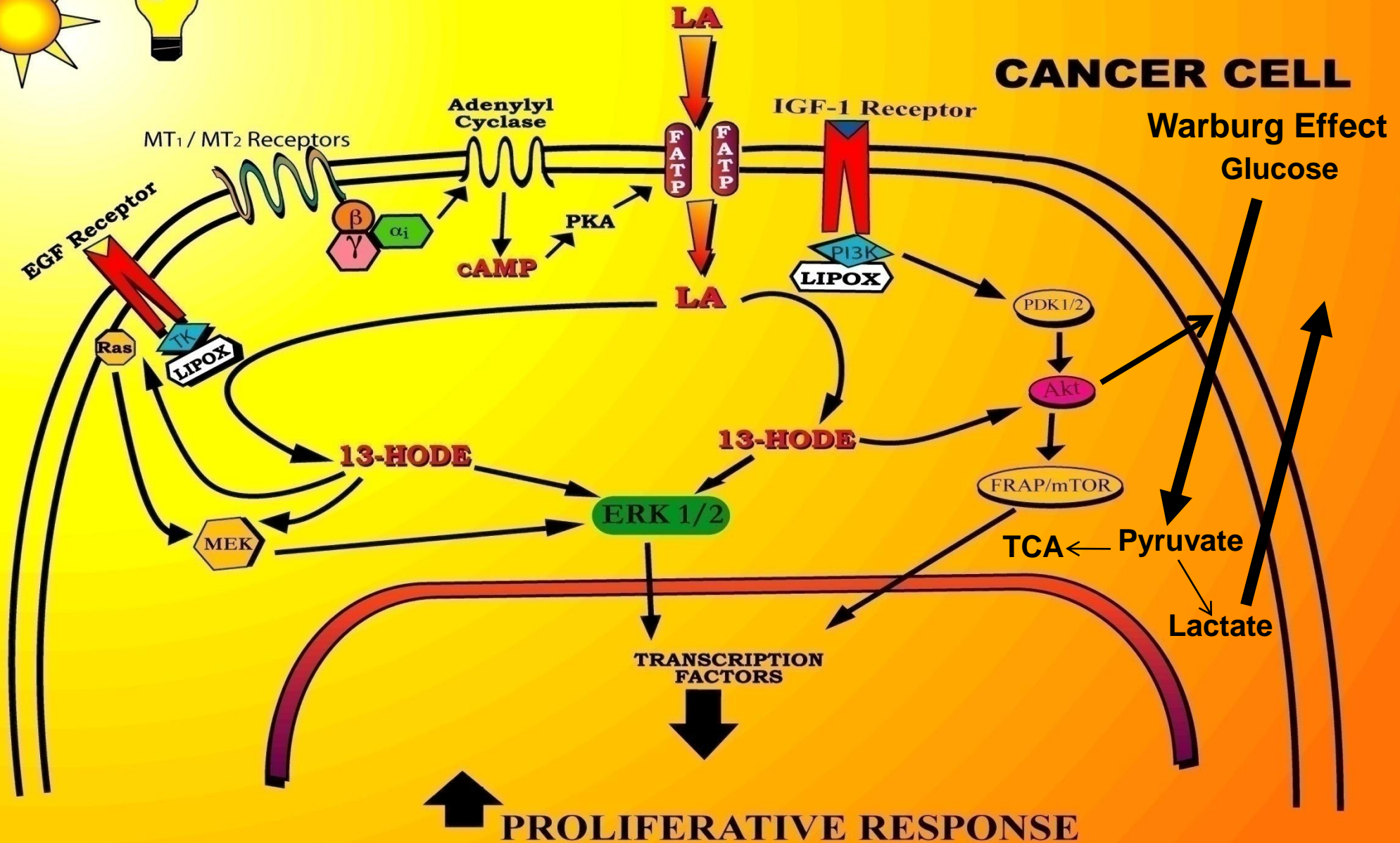
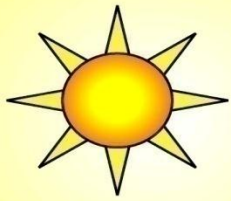
- **Direct antiproliferative and/or pro-apoptotic effects**
- **Indirect effects via neuroendocrine suppression of reproductive hormone production**
- **Antioxidant/free radical scavenging effects**
- **Enhancement of immune activity**

SYSTEM FOR PERFUSION OF TISSUE-ISOLATED TUMORS *IN SITU*

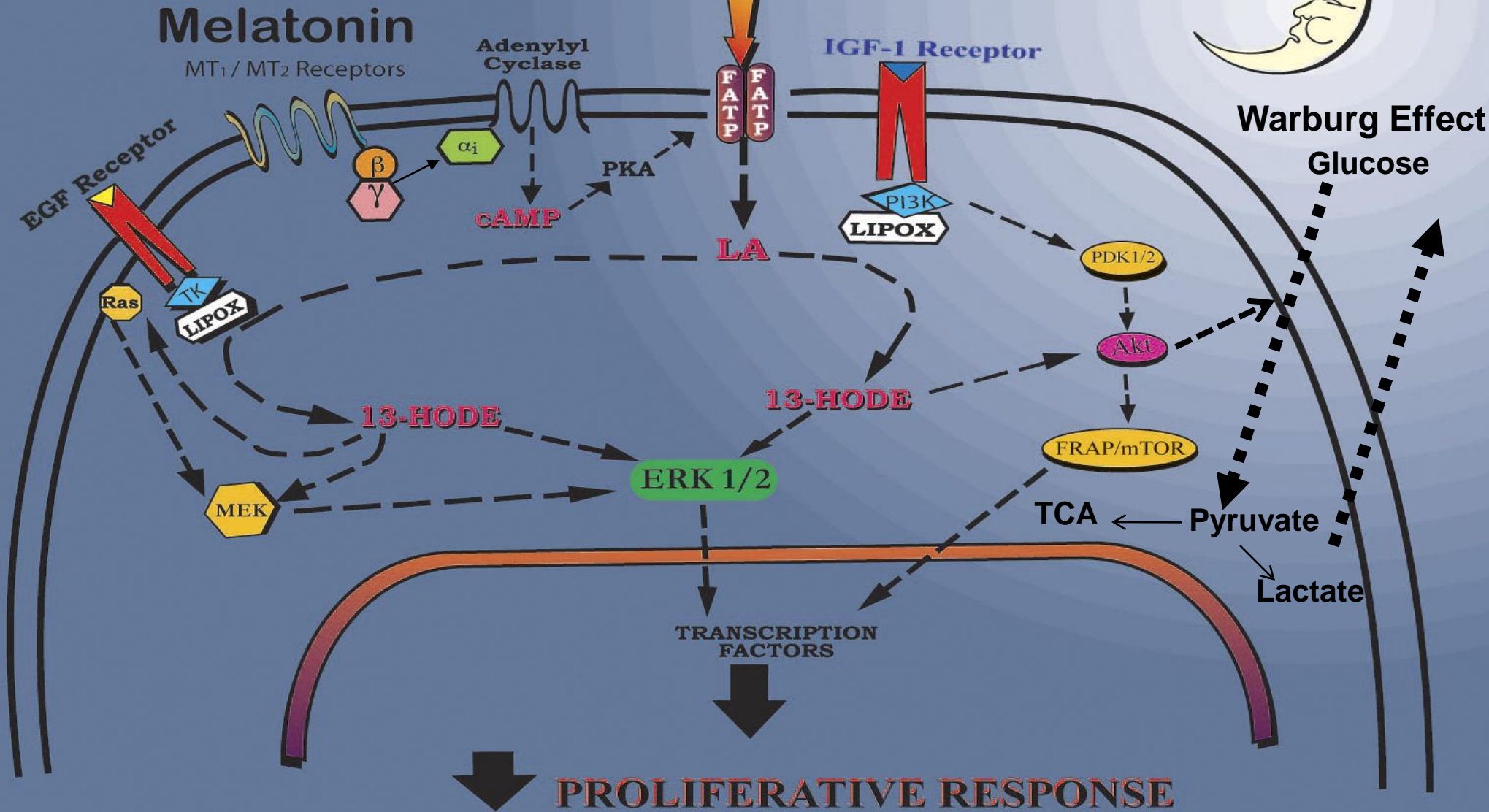


EFFECT OF MELATONIN ON FATTY ACID UPTAKE AND 13-HODE RELEASE
IN A MCF-7 HUMAN MAMMARY CANCER XENOGRAFT PERFUSED IN SITU





CANCER CELL



LIGHT DURING THE NIGHT

BAD!!!



PHOTOBIOLOGICAL EXPOSURE CHAMBER

Total Darkness

0.02 $\mu\text{W}/\text{cm}^2$

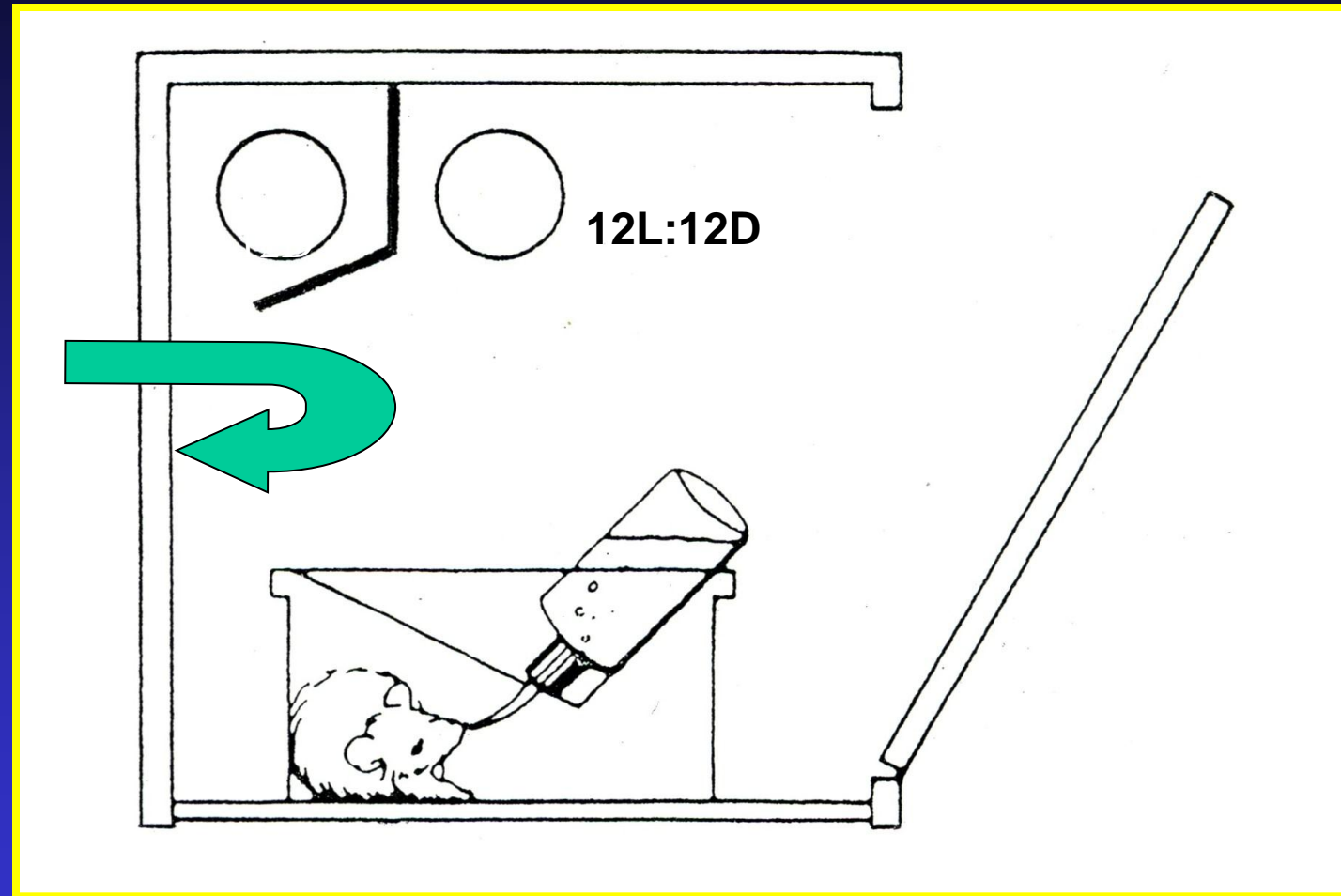
0.05 $\mu\text{W}/\text{cm}^2$

0.06 $\mu\text{W}/\text{cm}^2$

0.08 $\mu\text{W}/\text{cm}^2$

345 $\mu\text{W}/\text{cm}^2$

Reflected light at
rodent eye level for
2 wks prior to and
throughout tumor
growth period.

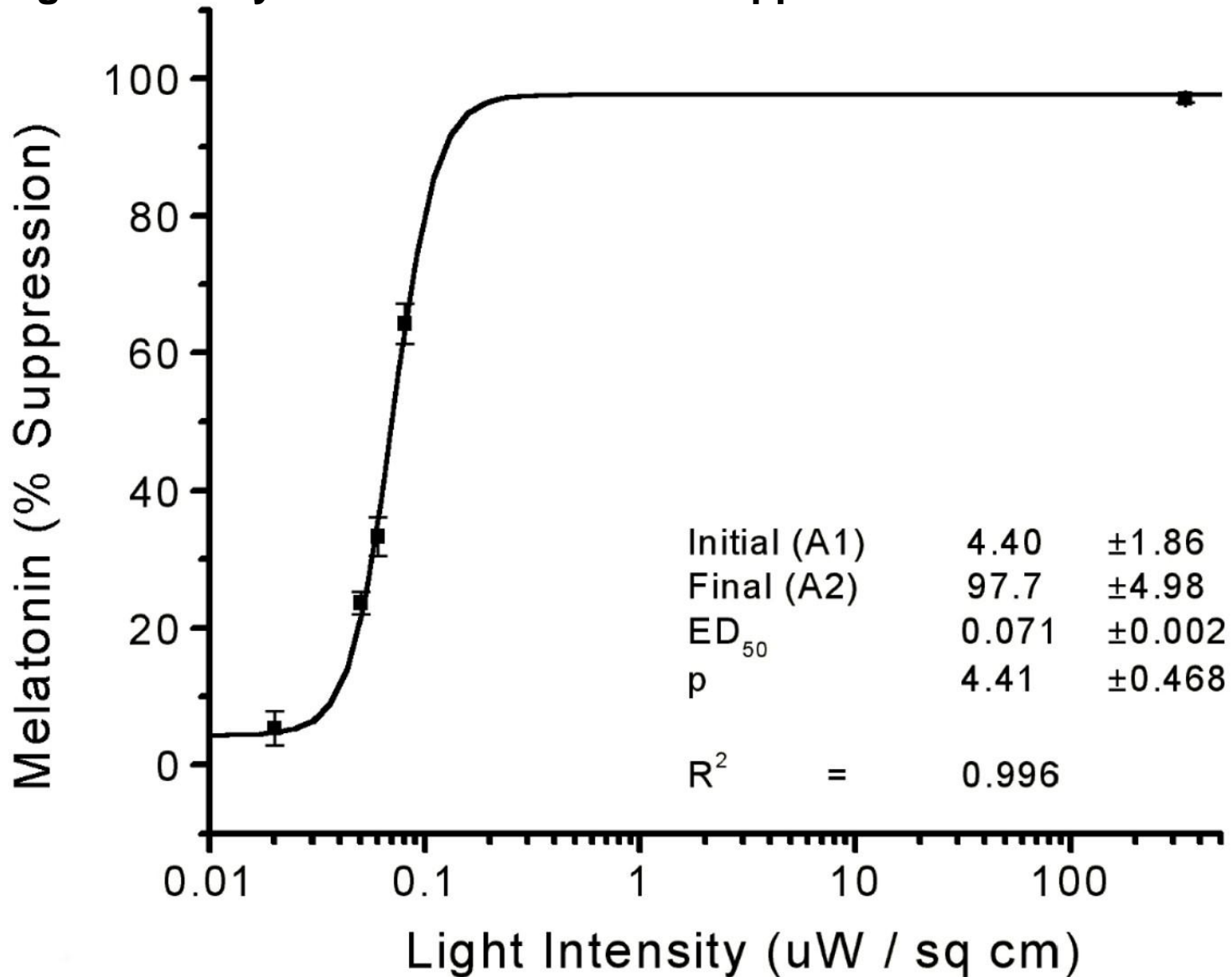




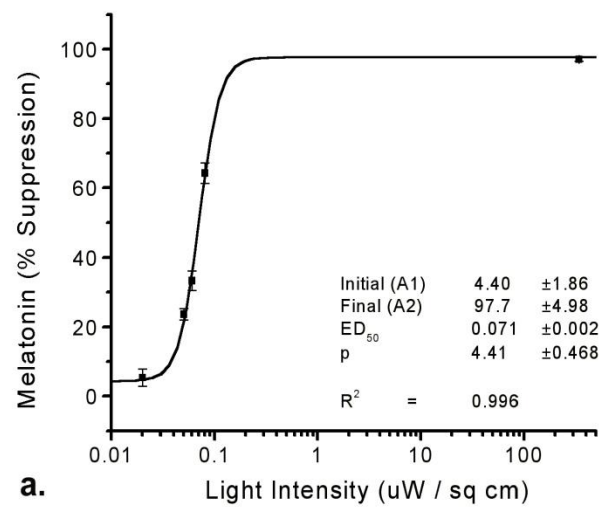
0.08 $\mu\text{W}/\text{cm}^2$ or 0.2 lux, or 0.02 ft.-candles

MELATONIN FLUENCE-RESPONSE CURVE - FEMALE NUDE RATS

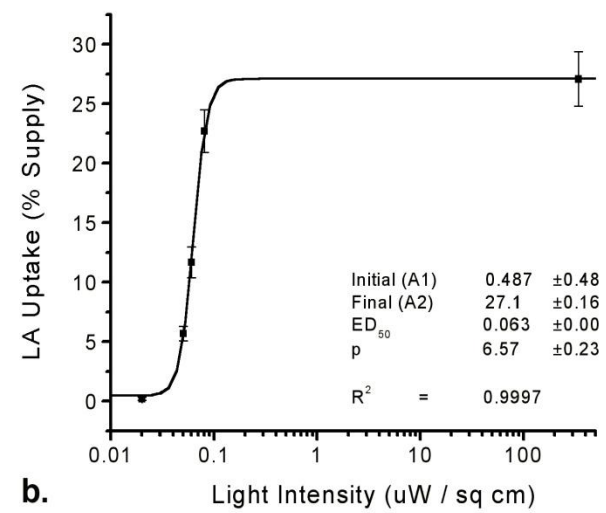
Light Intensity vs Percent Melatonin Suppression from Dark Condition



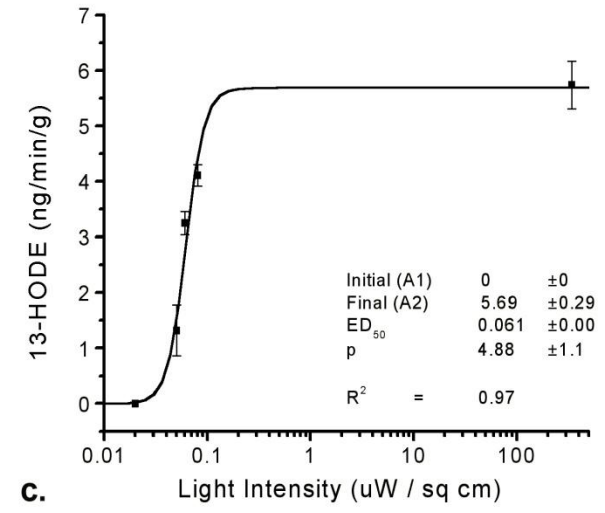
FLUENCE-RESPONSE CURVES FOR HUMAN BREAST CANCER XENOGRAFTS (MCF-7 SR-)



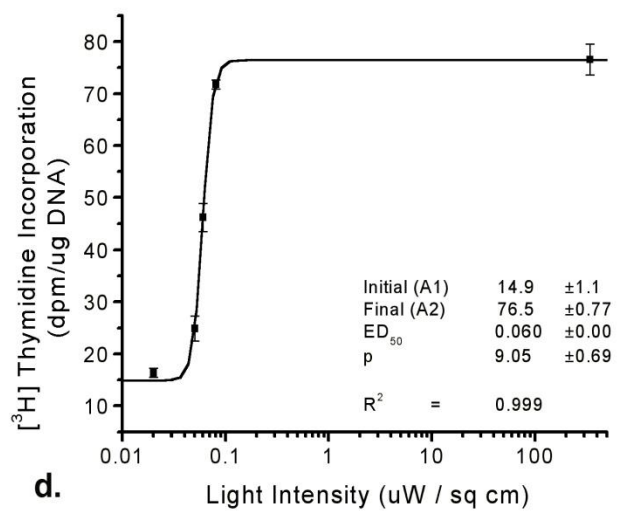
a.



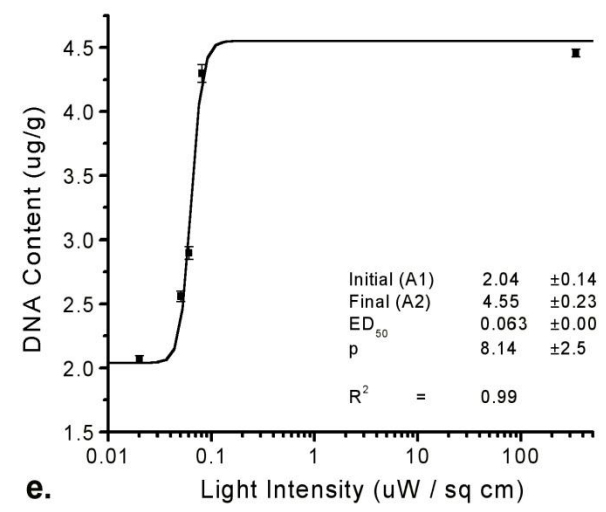
b.



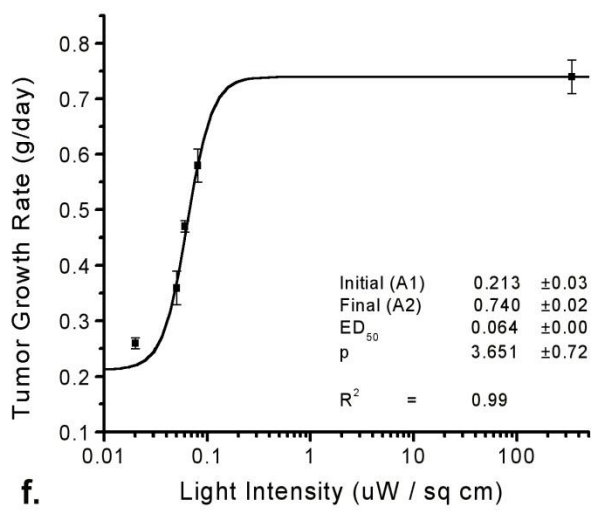
c.



d.

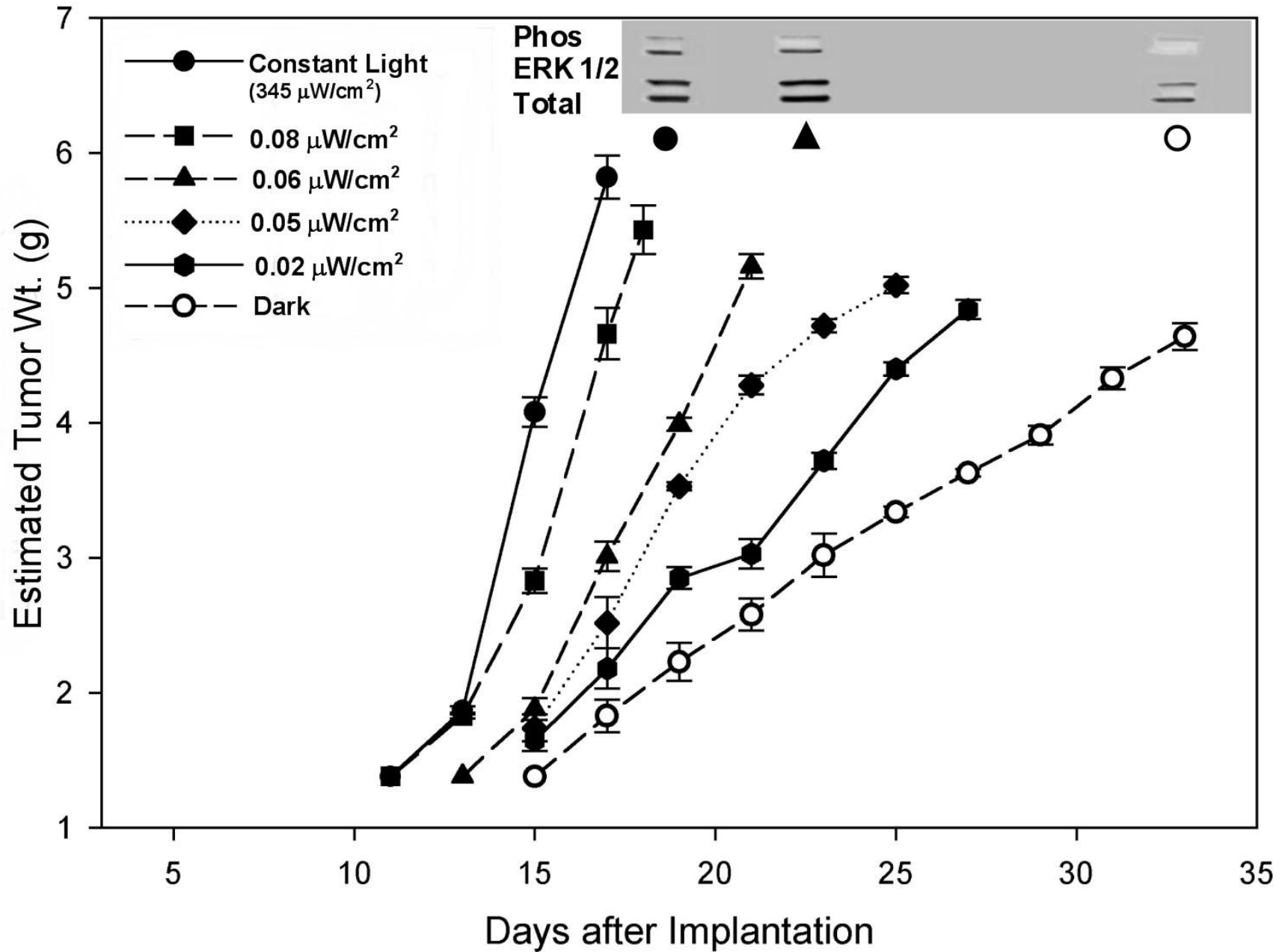


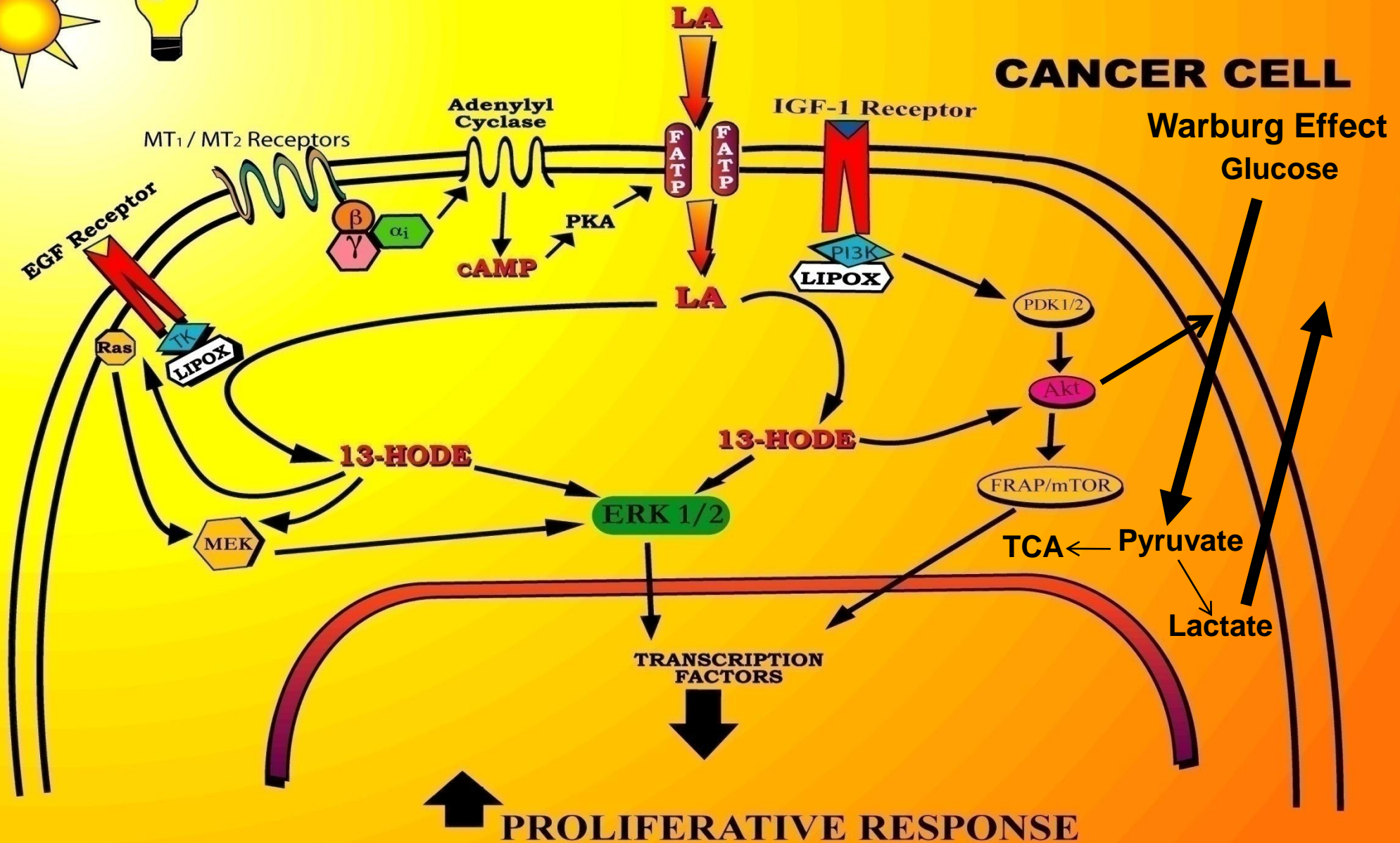
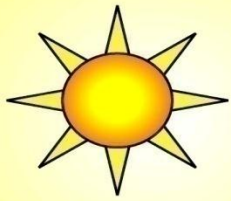
e.



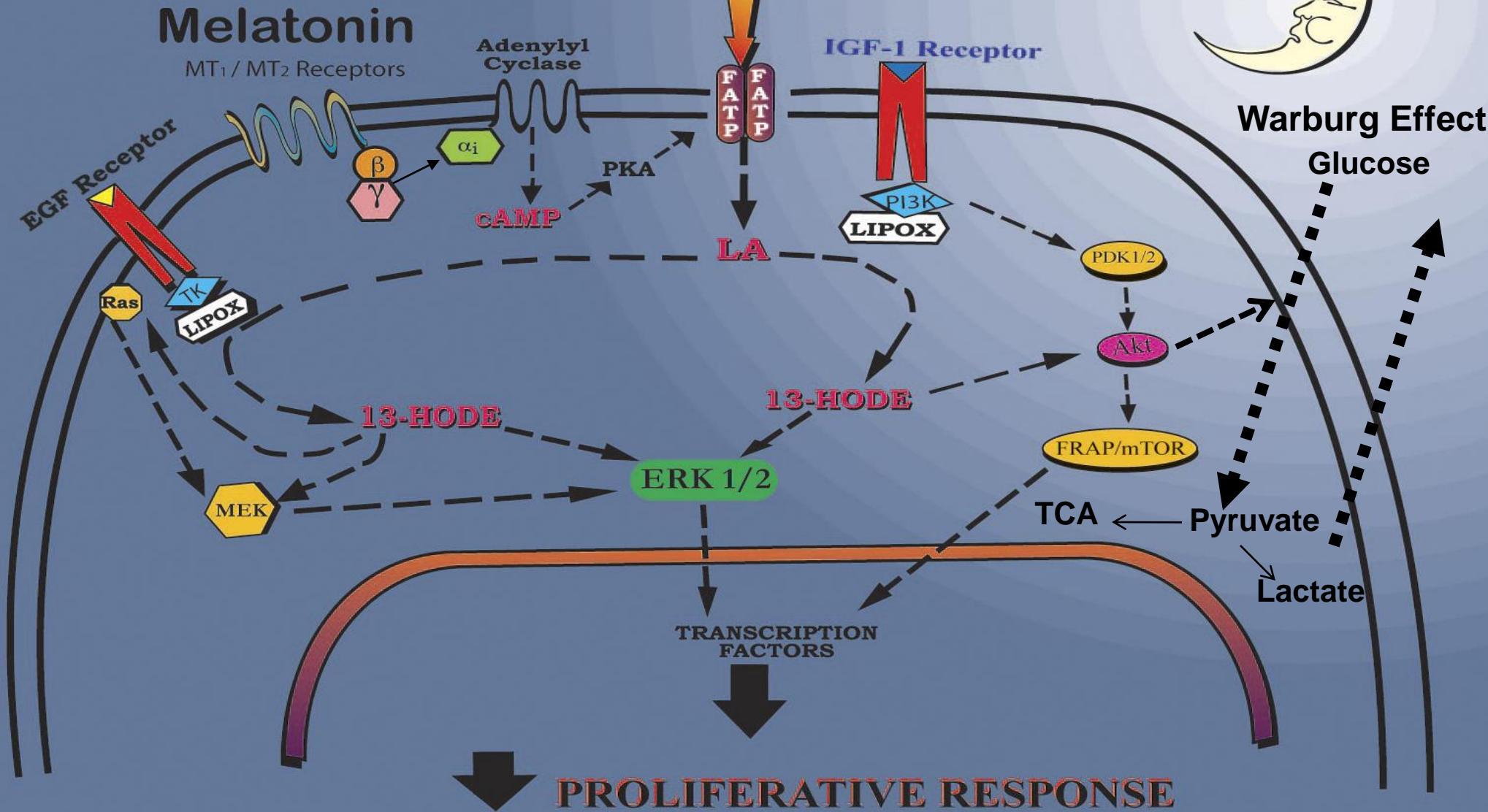
f.

GROWTH RATES VS LIGHT INTENSITY FOR HUMAN BREAST CANCER XENOGRAFTS



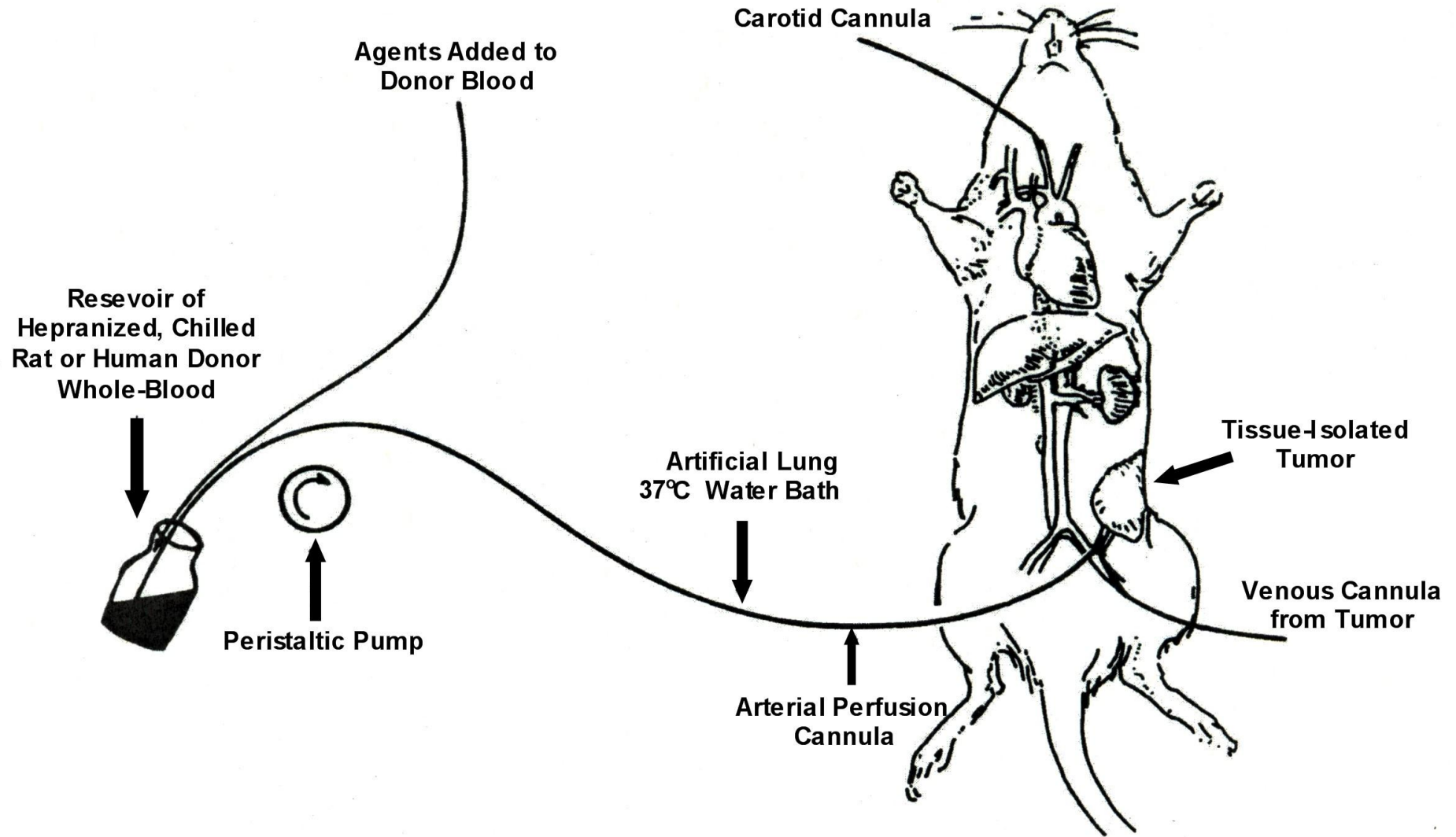


CANCER CELL

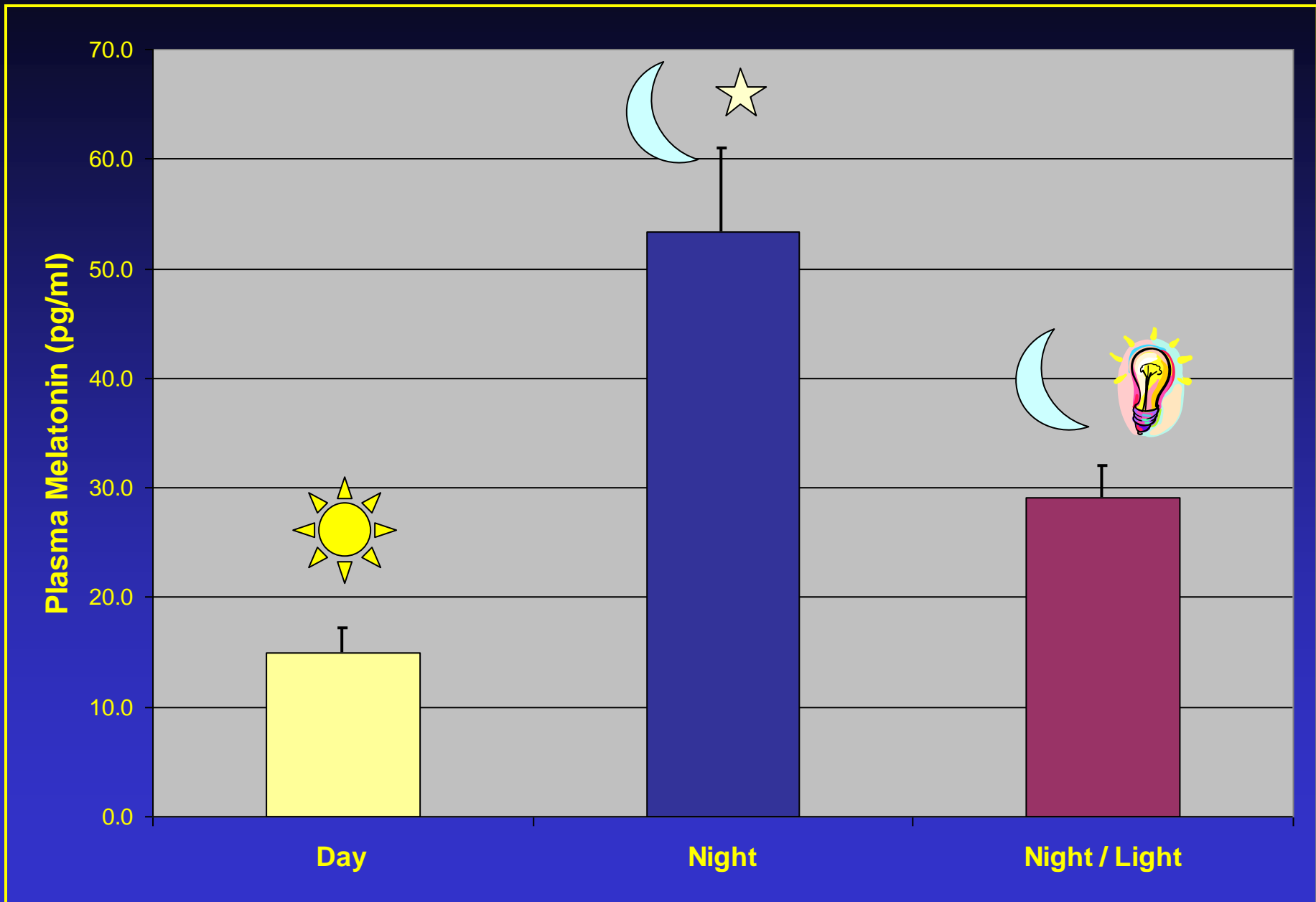




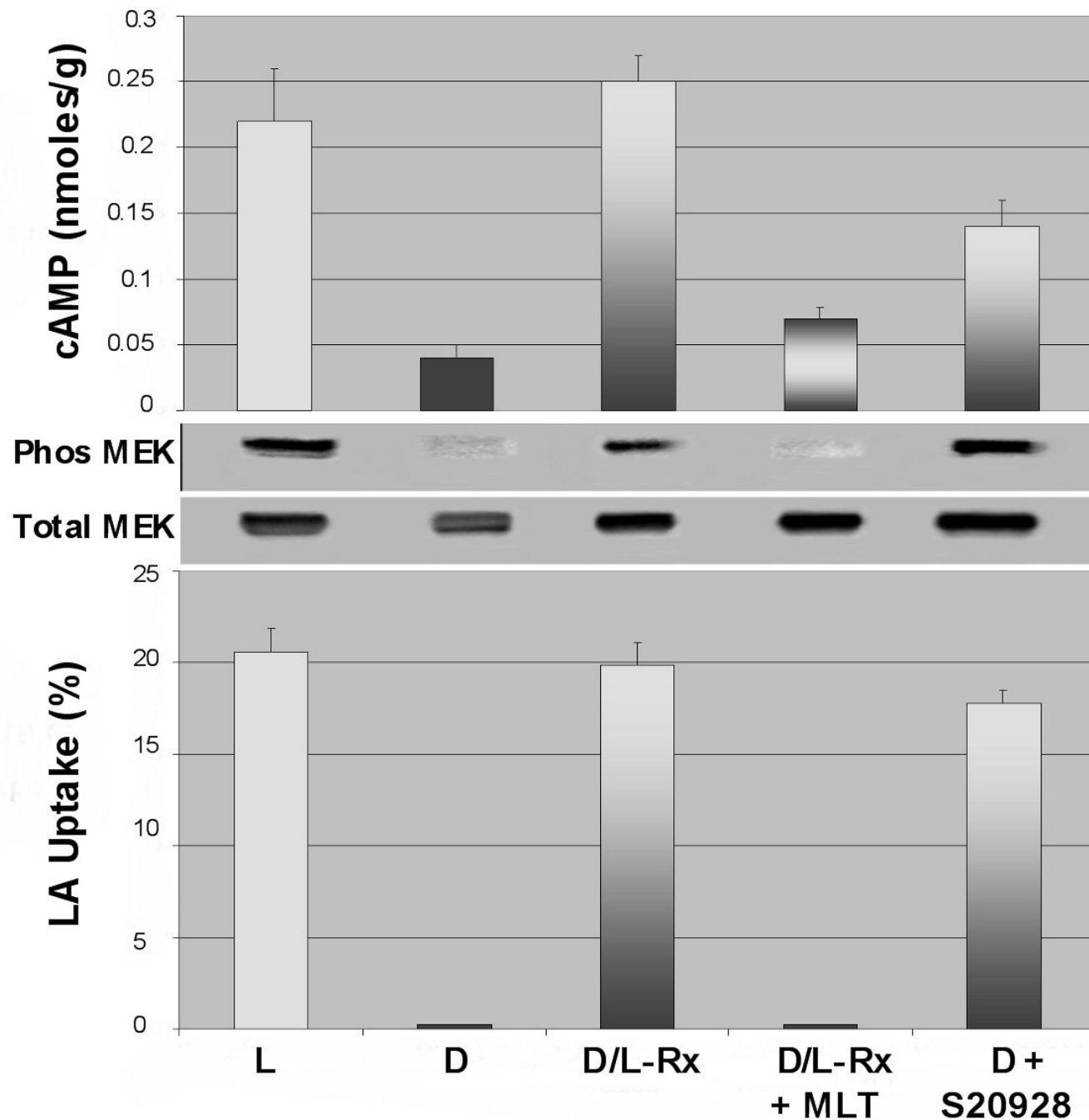
SYSTEM FOR PERFUSION OF TISSUE-ISOLATED TUMORS *IN SITU*



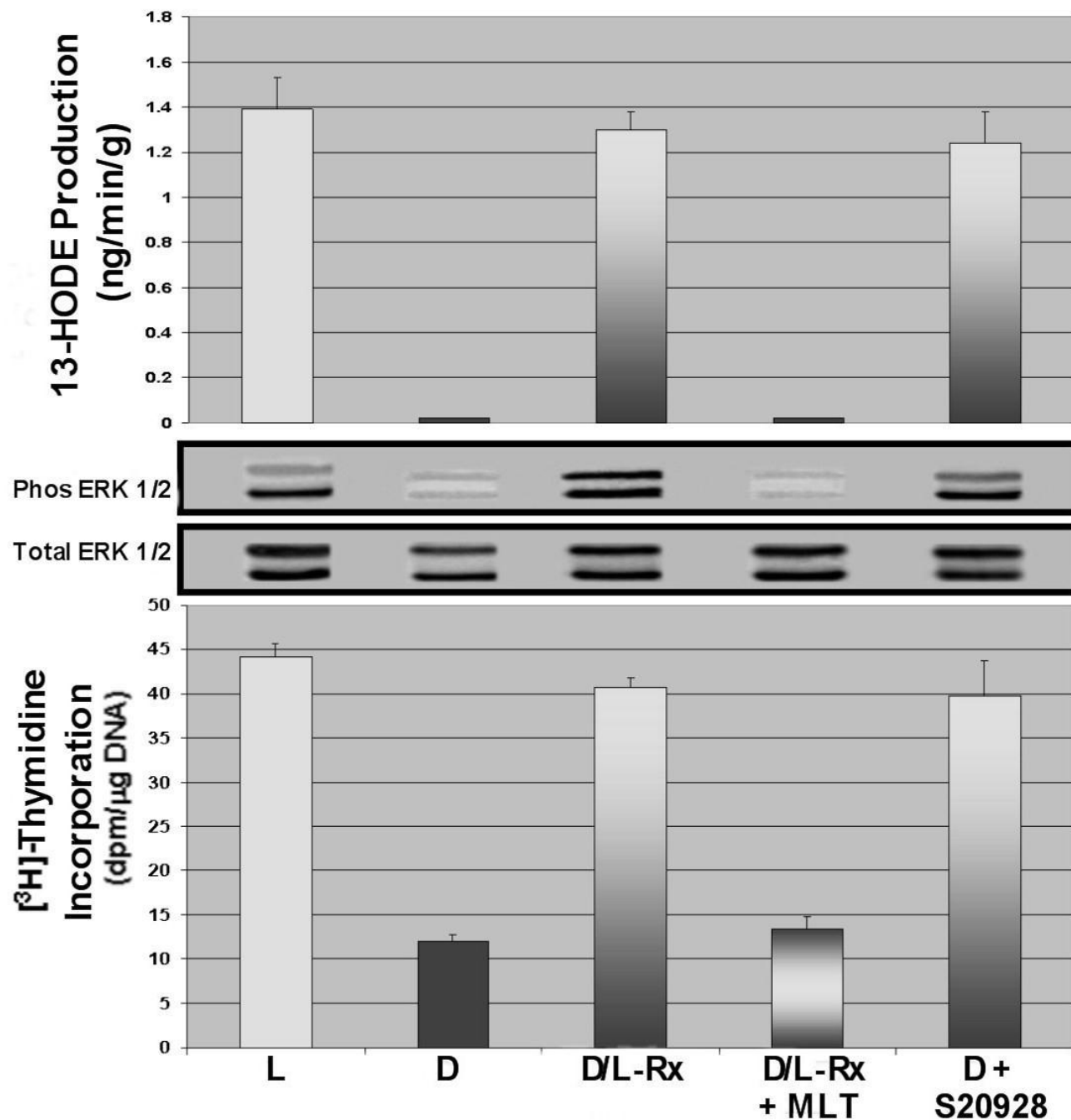
HUMAN BLOOD PLASMA MELATONIN LEVELS BEFORE AND AFTER LEAN



**SIGNAL TRANSDUCTION
AND PROLIFERATIVE
ACTIVITY IN MCF-7 (SR-)
HUMAN BREAST
CANCER XENOGRAFTS
PERFUSED *IN SITU* WITH
BLOOD COLLECTED
FROM HUMAN
VOLUNTEERS (n = 4)**



**SIGNAL TRANSDUCTION
AND PROLIFERATIVE
ACTIVITY IN MCF-7 (SR-)
HUMAN BREAST
CANCER XENOGRAFTS
PERFUSED *IN SITU* WITH
BLOOD COLLECTED
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VOLUNTEERS**



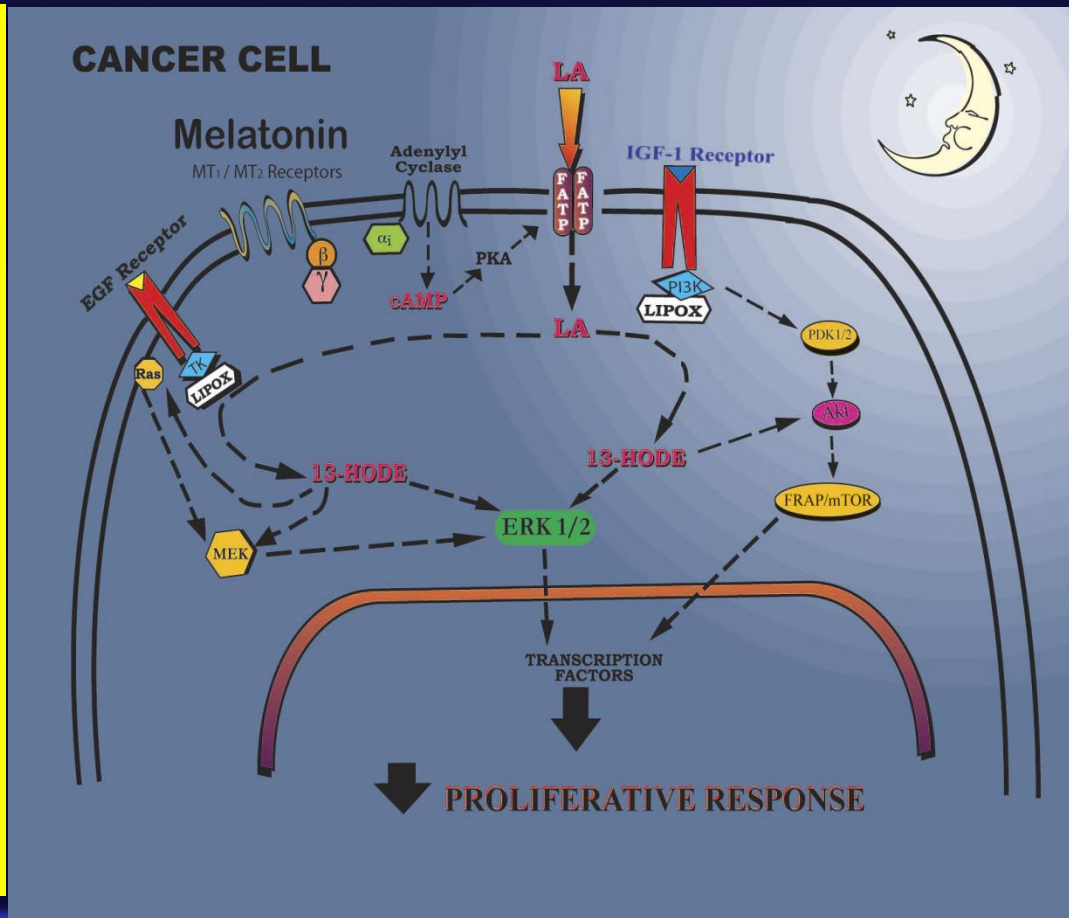
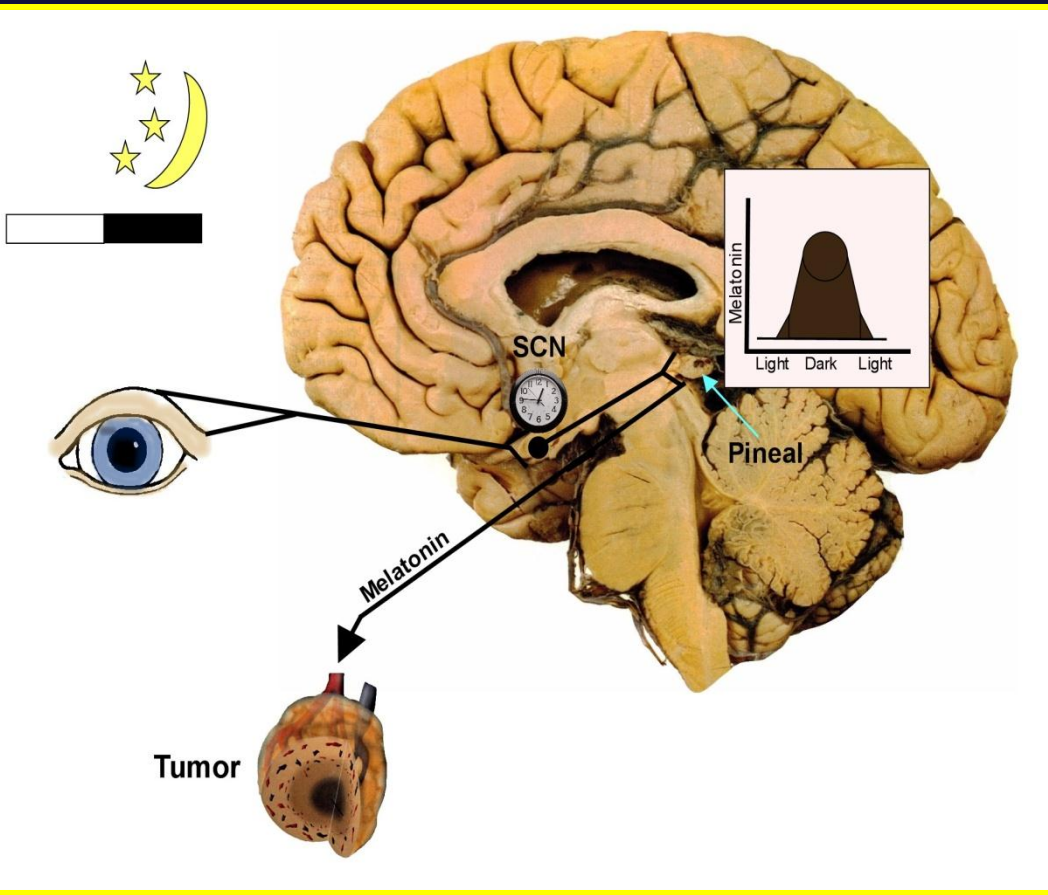
Mechanisms of Melatonin's Anti-Cancer Action

- Inhibition of nutrient, hormonal or growth factor stimulation of proliferation
- Inhibition of cell cycle progression (G_0 -S phase) with lengthening of cell cycle
- Inhibition of DNA synthesis
- Inhibition of cyclin-dependent kinases (e.g., cyclin D1)
- Stimulation of tumor suppressor gene expression (e.g., p53)
- Inhibition of oncogene expression (i.e., c-Myc)
- Inhibition of apoptosis
- Inhibition of invasion and metastasis and modulation of cytoskeletal and surface protein expression (e.g., \uparrow E-cadherin and Beta-1 Integrin)
- Stimulation of gap jct formation and intercellular communication
- Inhibition of telomerase
- Inhibition of aromatase

Other Mechanisms of Melatonin's Anti-Cancer Action

- Free radical scavenger
- Stimulation of Anti-Oxidant Enzyme Systems (i.e., glutathione)
- Inhibition of DNA damage, mutations, genetic instability, stimulation of DNA repair
- No effects on reproductive hormone secretion
- Enhances immune activity – pinealectomy or LAN decreases immune function
- Modulates core clock gene expression and expression of clock-related genes

LIGHTS OFF AT NIGHT



LIGHTS ON AT NIGHT

