Where Will Our New Therapeutics Come From?

Professor Paul F. Long
Faculty of Life Sciences & Medicine - KCL
Faculdade de Ciências Farmacêuticas - USP

Outline For This Morning

- Some considerations on the current state of the pharmaceutical industry
- Coffee
- ‘Adventures’ in marine biology

Why are Drugs Important?

1. Health of the Nation

e.g., Devastation caused by Malaria, Aids, Cholera, Ebola *etc* in Africa. Developed countries are not so concerned simply with survival. Even less serious diseases such as influenza can cause chaos in the developed world.

2. Economy

e.g., ~25% of total UK R&D budget (Greater than for any other Industrial Sector)

3. International Prestige (*e.g.,* GSK, AZ)

gsk do more feel better live longer

"Healthy Nation is a Prosperous Nation"

Health of a nation through four generations

Victorian

Life Expectancy	41(M) 43(F)
Main cause of death	Tuberculosis
Drink (litres of pure alcohol per year)	12
Smoking (kg per person per year)	zero
Age at marriage (women)	24
Population under 15(%)	36
Population over 64 (%)	5
Divorce rate per 1,000 couples	0

Edwardian

Life Expectancy	45(M) 49(F)
Main cause of death	Tuberculosis
Drink (litres of pure alcohol per year)	7
Smoking (kg per person per year)	6
Age at marriage (women)	25
Population under 15(%)	30
Population over 64 (%)	5
Divorce rate per 1,000 couples	0

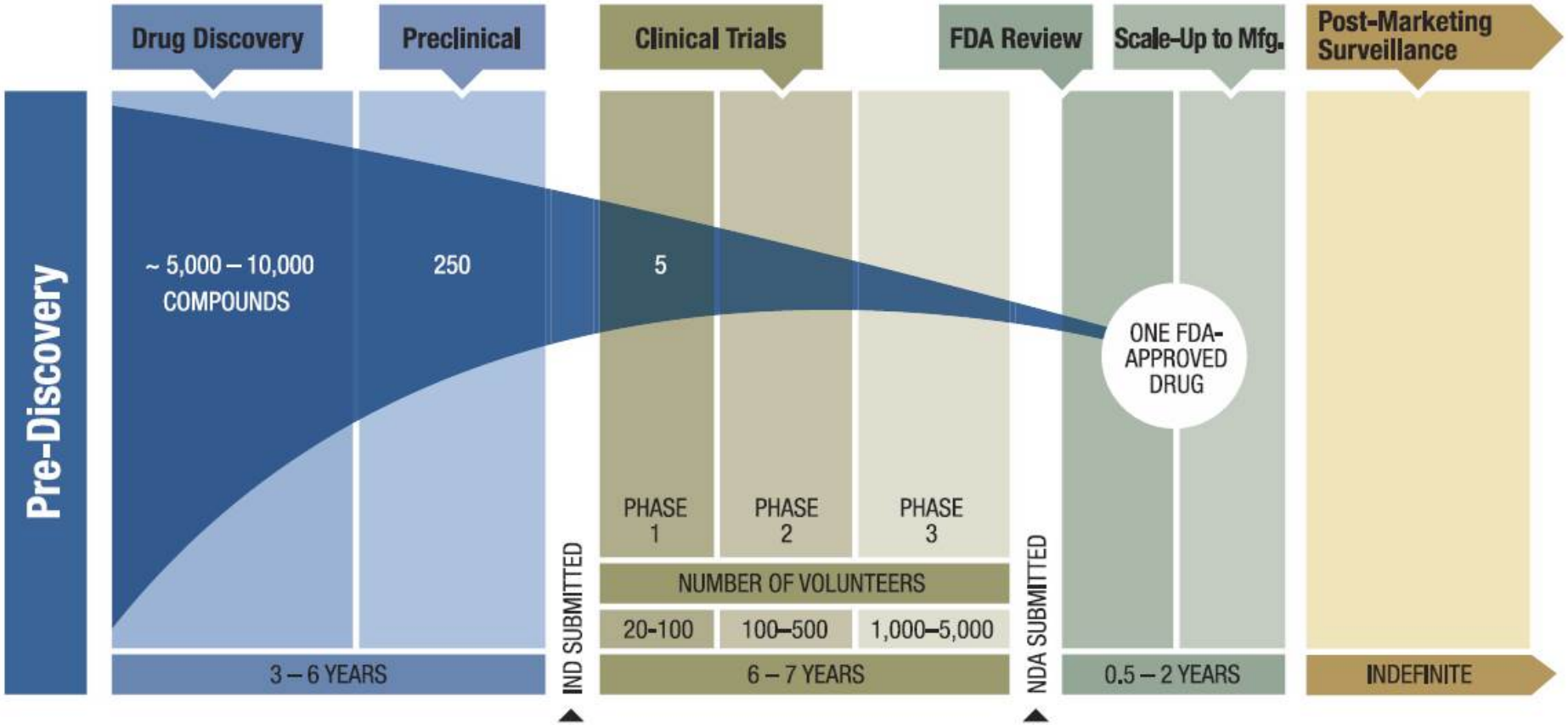
1940's

Life Expectancy	68(M) 74(F)
Main cause of death	Heart disease
Drink (litres of pure alcohol per year)	4
Smoking (kg per person per year)	11
Age at marriage (women)	23
Population under 15(%)	22
Population over 64 (%)	10
Divorce rate per 1,000 couples	100

Present

Life Expectancy	73(M) 79(F)
Main cause of death	Cancer\Heart disease
Drink (litres of pure alcohol per year)	7
Smoking (kg per person per year)	3
Age at marriage (women)	26
Population under 15(%)	19
Population over 64(%)	16
Divorce rate per 1,000 couples	500

Drug Discovery and Development Timeline



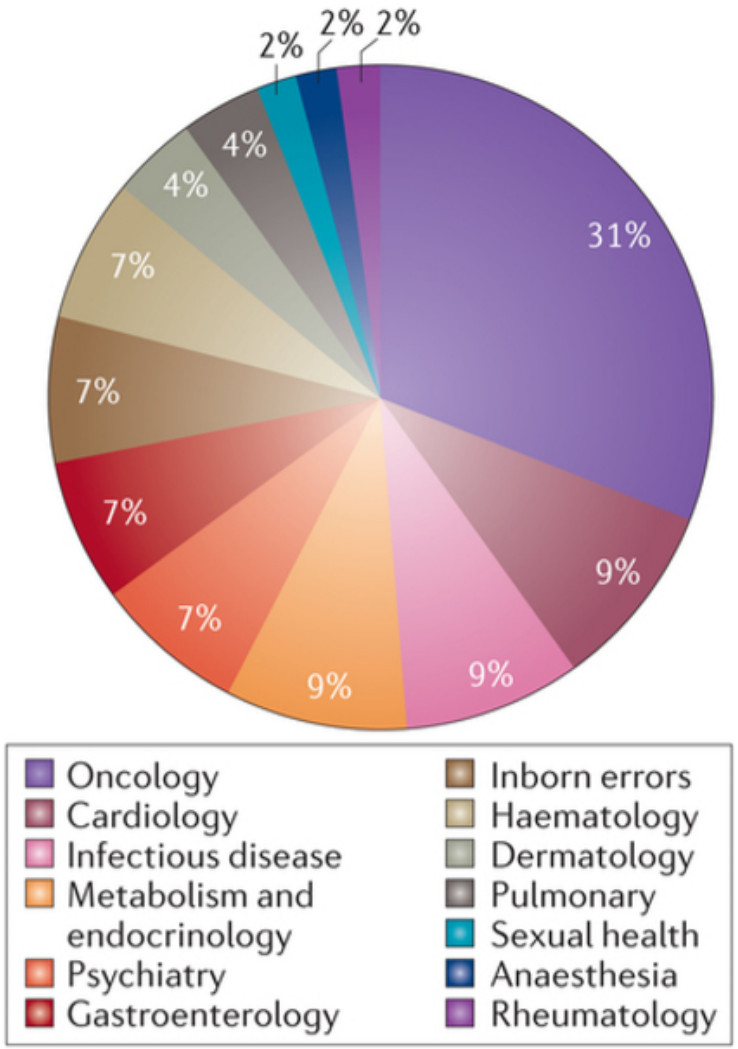
The creation of a new drug can be broadly divided into three main phases:

- **Drug discovery – from therapeutic concept to molecule**
- Drug development – from molecule to registered product
- Commercialisation – from product to therapeutic application to sales.

How Many Drugs Are There?

- Between 1000-1500 individual drug substances are approved world-wide for medical use.
- Most of these are custom-designed synthetic compounds produced by the drug discovery programmes of pharmaceutical companies.
- In the last few years, approximately 20-30 new compounds have been approved every year in the UK.

FDA Approvals by Therapeutic Area in 2015



Nature Reviews | Drug Discovery

How Therapy is Delivered by 'Big Pharma'

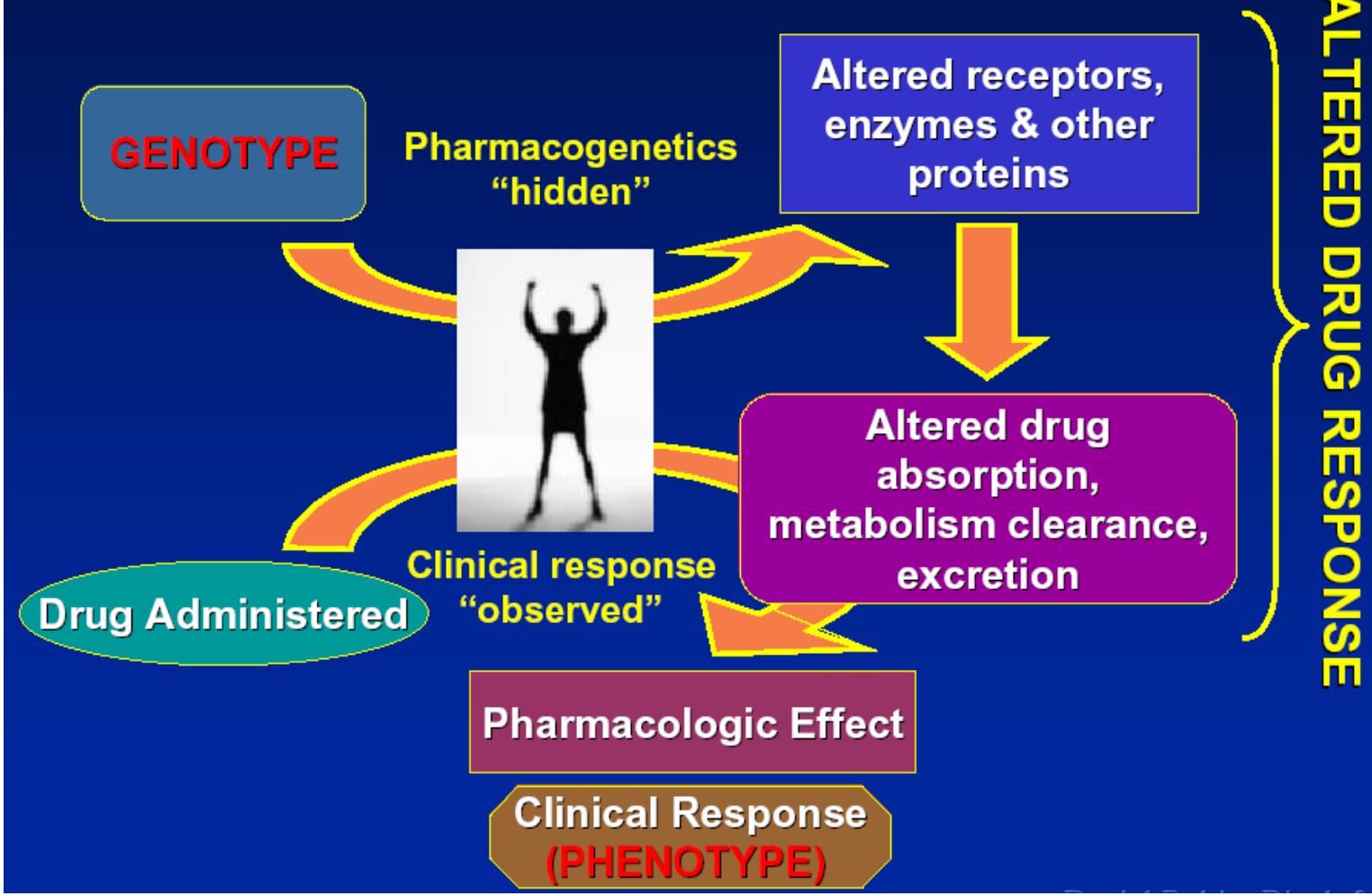
"One Size Fits All" Approach to Drug Therapy

- This means that a patient may not receive the optimal drug and/or dosing for their disease.
  - The drug prescribed may lead to ADRs which can be life-threatening.
  - Even worse: Drug may not work at all wasting time and causing further distress to patient!

But we are not all the same: gender, age, ethnicity, height/weight, general health, genotype.....all influence drug PK/ADME

The Future: Personalised Medicines Based on Pharmacogenomics

Connecting Variations in Genotype & Phenotype

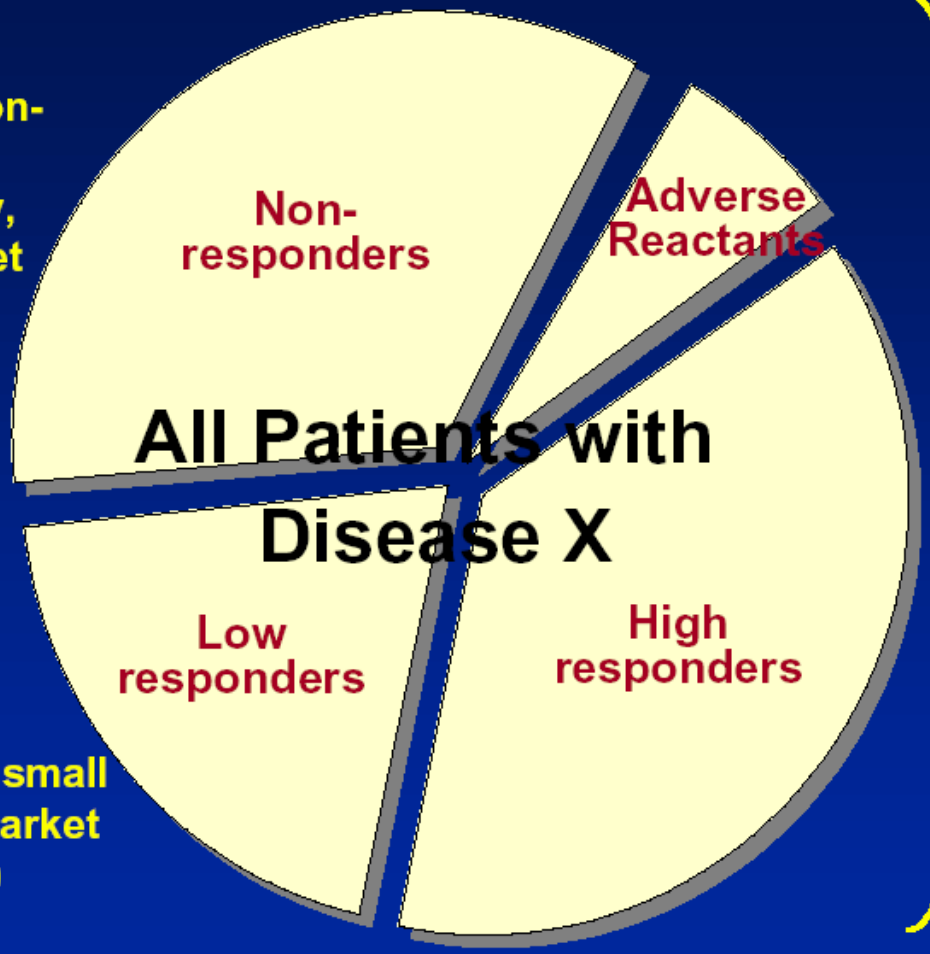


Market Segmentation

Drug B:
Tailored to non-responders; Good efficacy, smaller market

NO AE's!

Drug C:
Drug for very small specialized market (orphan drug)

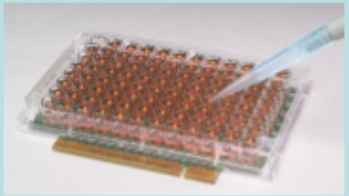


Drug A:
SINGLE drug for "average" patient; large market, but *efficacy varies*

Drugs based on pharmacogenetics

Current drug development

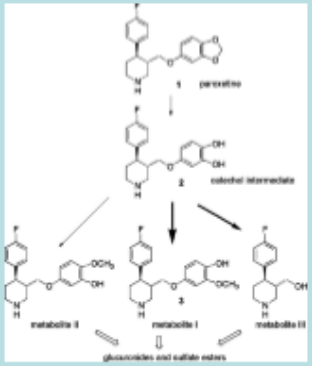
Where Do New "Lead" Agents Come From?



Screening (Phenotypic)
(Synthetic, Natural Products, Existing drugs for Re-Positioning)

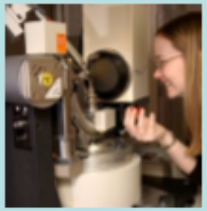
Natural Products

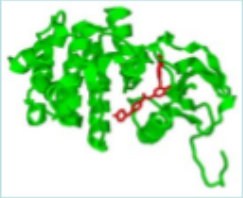
Side Effects
(Clinical Observation; Re-Positioning)



Metabolism Studies

Serendipity
(Chance Observation)





Rational Drug Design
(Structural Biology/Screening/ Molecular Modeling/Synthesis)

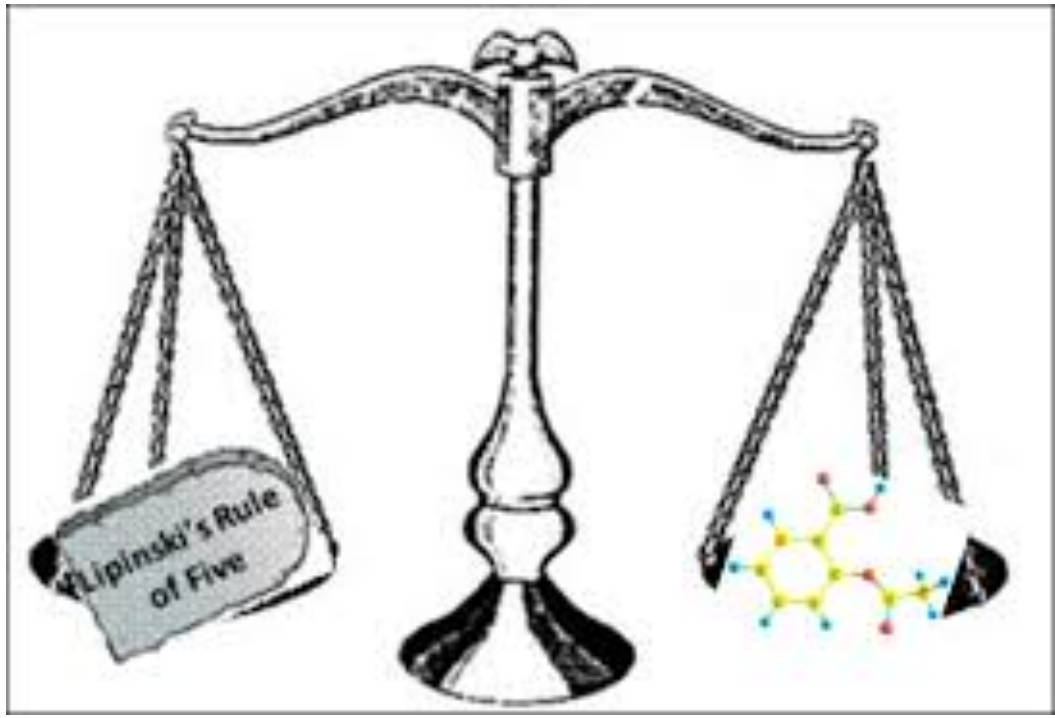
Small Molecules

Biologics

Drugability: The Lipinski "Rule of Five"

A potential drug molecule will have poor absorption and distribution properties if:

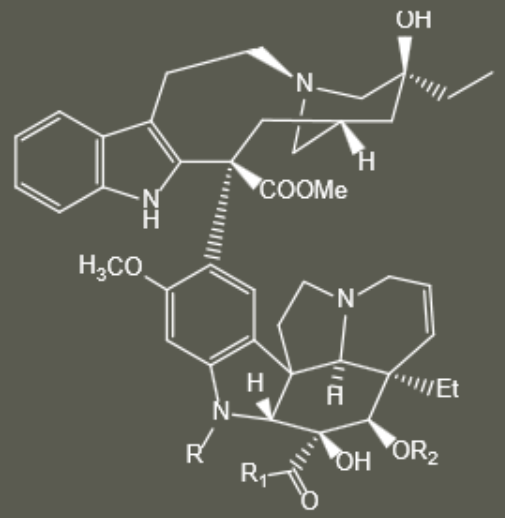
- Molecular weight is >500
- Calculated log P > 5
- 5 hydrogen-bond donors
- > 10 hydrogen-bond acceptors



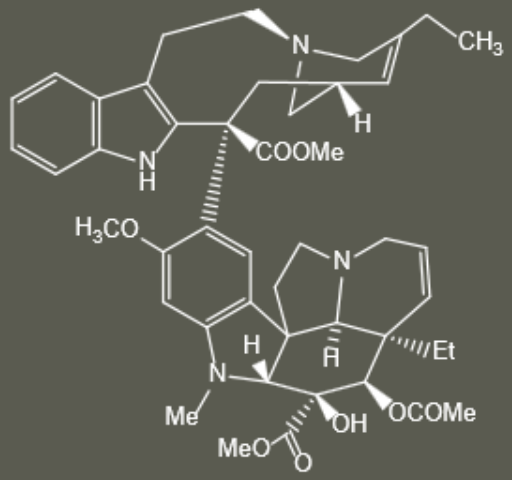
Other examples of clinically-useful drugs outside of Lipinski's Rules

Madagascar periwinkle

(*Vinca rosea*)



	R	R_1	R_2
Vinblastine (Velbe™)	Me	OMe	COMe
Vincristine (Oncovin™)	CHO	OMe	COMe
Vindesine (Eldesine™)	Me	NH_2	H



Vinorelbine (Navelbine™)

Vinca Alkaloids

Vinblastine
M.Wt. 810.97

Pharmacological Treatments: Small-Molecule Drugs

Either synthetic compounds or natural products, have for a long time been the mainstay of therapeutics and are likely to remain so, despite the rapid growth of biopharmaceuticals in recent years.

- Advantages
  - 'Chemical space' is so vast that chemicals have the potential to bind specifically to any chosen biological target: the right molecule exists; it is just a matter of finding it.
  - Doctors & patients are thoroughly familiar with conventional drugs as medicines and, the many different routes of administration that are available. Oral administration is often possible.
  - Although sections of the public may remain suspicious of drugs, there are few who will refuse to use them when the need arises.
  - Pharmaceutical companies have long experience in developing, registering, producing, packaging and marketing such products.

Pharmacological Treatments: Small-Molecule Drugs

- Disadvantages
  - The discovery of new small-molecule drugs seems to be diminishing, despite increasing R&D expenditure.
  - Side effects and toxicity remain a serious and unpredictable problem, causing failures in late development, or even after registration. One reason for this is that the selectivity of drug molecules with respect to biological targets is by no means perfect.
  - Humans have highly developed mechanisms for eliminating foreign molecules, so drug design often has to contend with pharmacokinetic problems.
  - Oral absorption is poor for many compounds.

The Rise of Biologics – Now a Driving Force in Pharma (2017)

TOP 10 PRODUCTS Gilead's Harvoni became a leading product within just one year

DRUG NAME	TYPE	MARKETER	INDICATION	ESTIMATED 2015 SALE ($ BILLIONS)	% CHANGE FROM 2014
Humira	Antibody	AbbVie, Eisai	Inflammation	14.2	13
Harvoni	Small molecule	Gilead Sciences	Hepatitis C	13.9	554
Enbrel	Protein	Amgen, Pfizer, Takeda	Inflammation	8.7	-2
Remicade	Antibody	Janssen, Merck & Co.	Inflammation	8.3	-10
Rituxan	Antibody	Roche	Cancer	7.0	3
Lantus	Peptide	Sanofi	Diabetes	6.9	2
Avastin	Antibody	Roche, Chugai	Cancer	6.6	4
Herceptin	Antibody	Roche	Cancer	6.5	5
Januvia/Janumet	Small molecule	Merck & Co.	Diabetes	6.2	3
Seretide	Small molecule	GlaxoSmithKline	Asthma	5.7	-11

NOTE: Foreign currencies converted at current exchange rates. **SOURCES:** Company data, stock analysts, and C&EN estimates

Biopharmaceuticals

- Biopharmaceuticals have been around for a long time - Immunization against infectious diseases dates from Jenner (smallpox, 1796).
- Biopharmaceuticals are therapeutic protein or nucleic acid preparations made by techniques involving recombinant DNA technology, although smaller nucleotide assemblies are now being made using a chemical approach (e.g. Synthetic biology and 'click' chemistries).
- This field has now matured to the point that we are now facing the prospect of 'bio-similars' (aka, 'generics') consequent on the expiry of the first set of important patents in 2004.

E. coli recombinant human insulin
(1982 Eli Lilly, Humulin)

Mammalian recombinant human erythropoietin
(1989 Amgen, EPO-α)
The most successful biotech drug in history: sales > US$ 2 billion 2007 in USA.

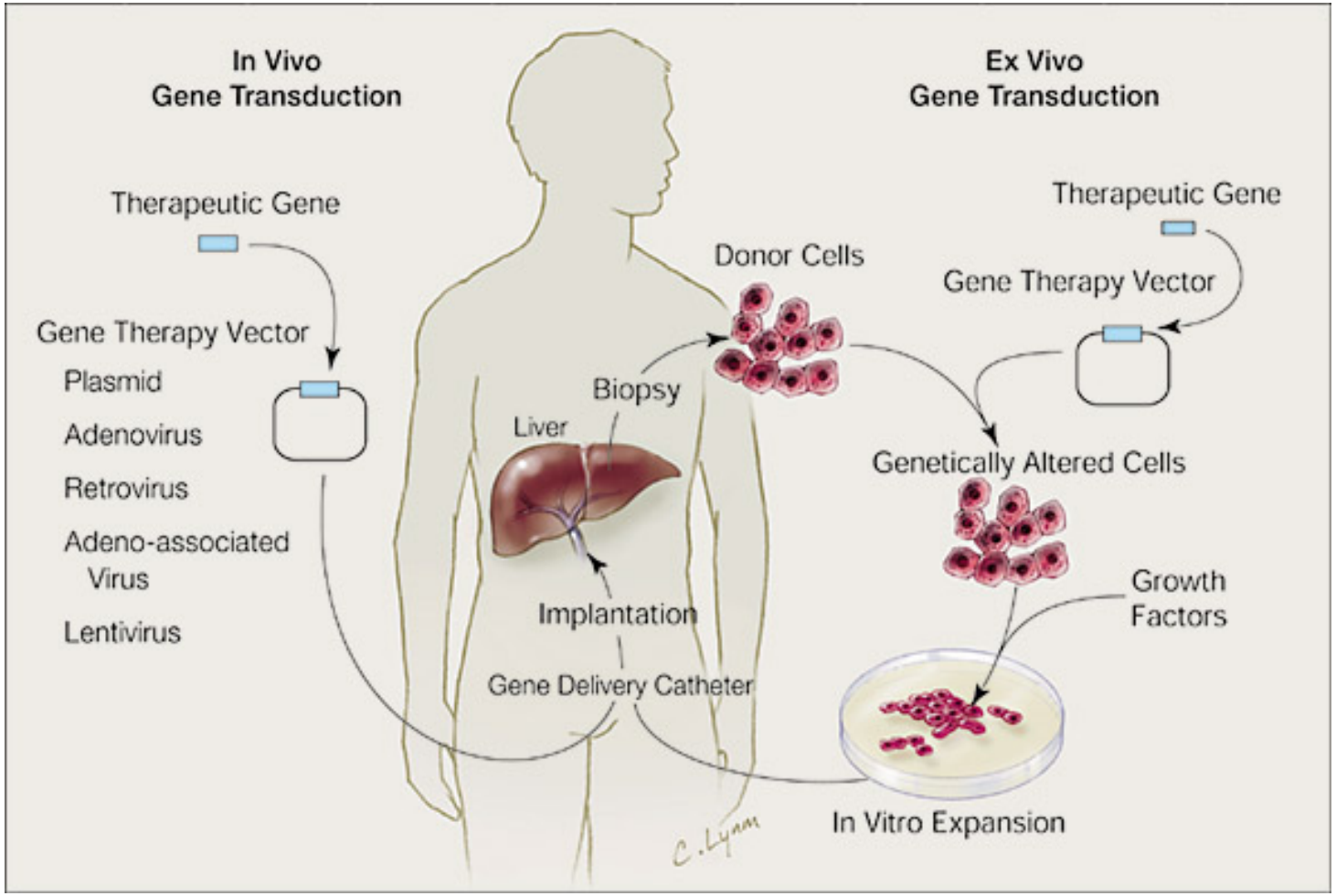
Biopharmaceuticals

- **Advantages**
  - The main benefit offered by biopharmaceutical products is that they open up the scope of protein therapeutics, which was previously limited to proteins that could be extracted from animal or human sources.
  - The discovery process for new biopharmaceuticals is often quicker and more straightforward than with synthetic compounds, as screening and lead optimization are not required.
  - Unexpected toxicity is less common than with synthetic molecules.
  - The risk of immune responses to non-human proteins – a problem with porcine or bovine insulin – is avoided by expressing the human sequence.
  - The risk of transmitting virus or prion infections is avoided.

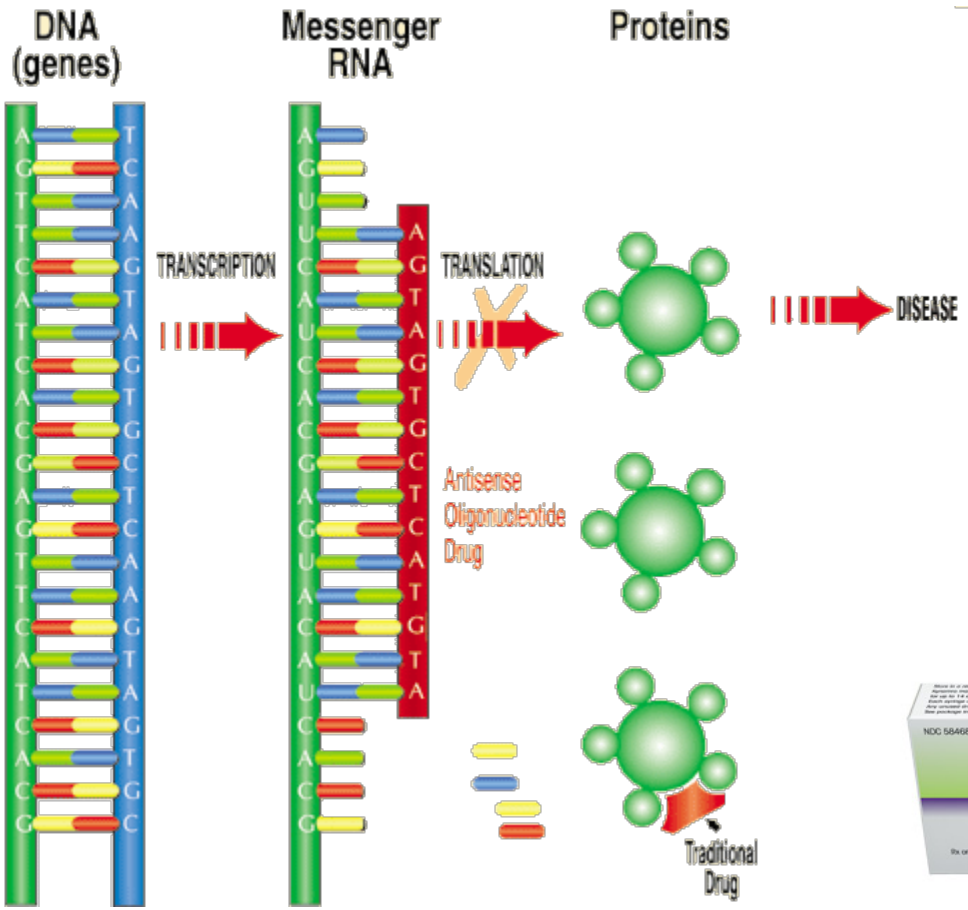
- **Disadvantages**
  - Producing biopharmaceuticals on a commercial scale is expensive, requiring complex purification and quality control procedures.
  - The products are not orally active and often have short plasma half-lives, so special delivery systems may be required, adding further to costs.
  - Like other proteins, biopharmaceutical products do not cross the blood–brain barrier.
  - For the above reasons, development generally costs more and takes longer, than it does for synthetic drugs.
  - Many biopharmaceuticals are species specific in their effects, making tests of efficacy in animal models difficult or impossible.

Gene Therapy

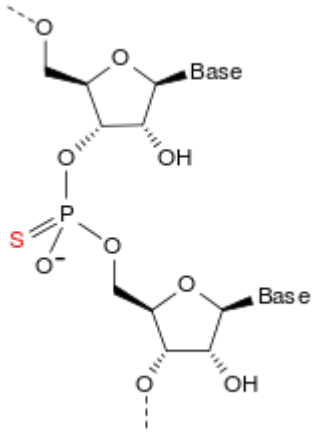
Recombinant DNA technology offers the promise of altering the genetic material of cells and thereby correcting the results of genetic defects, whether inherited or acquired.



Antisense Therapy

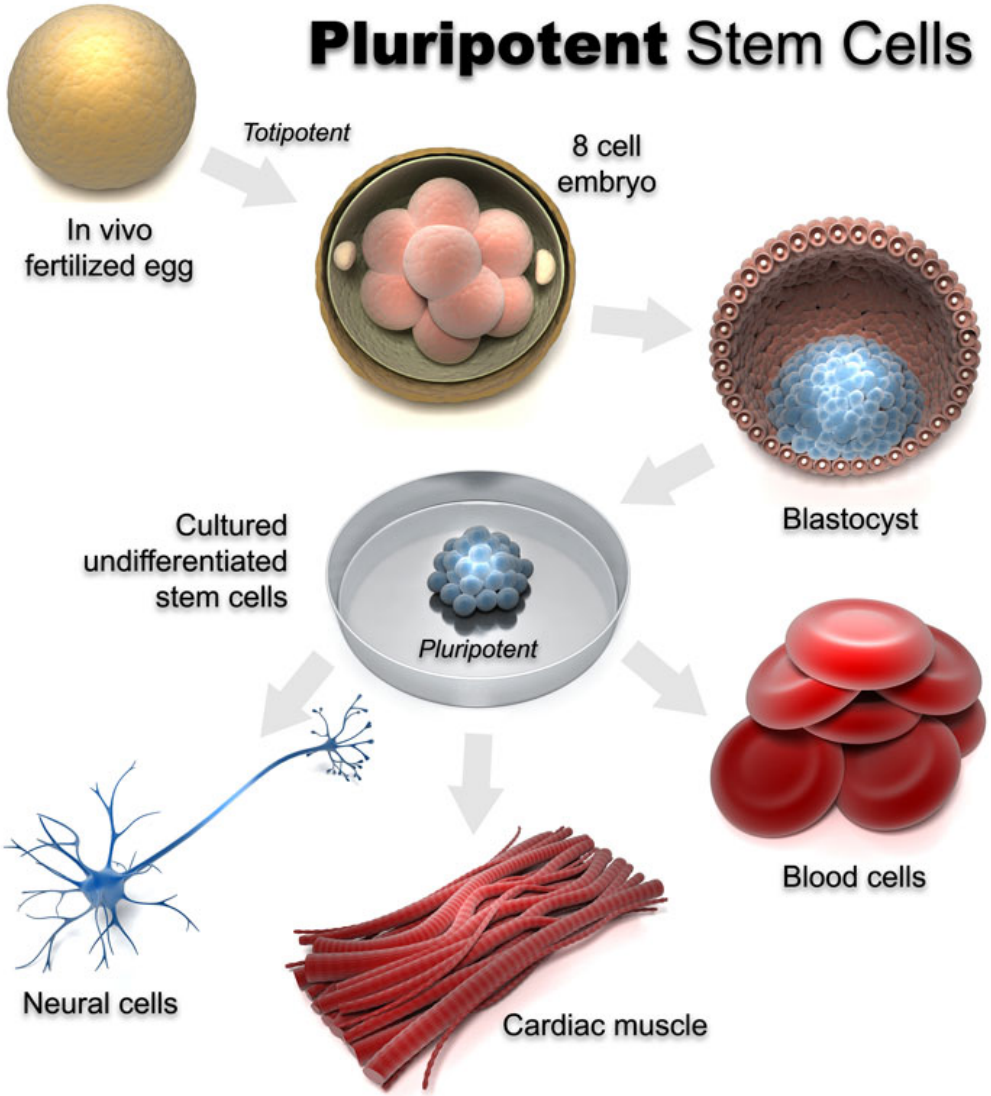


Isis Pharma / Ciba
(1998)
Cytomegalovirus
infection



Genzyme Corp. 2013
Homozygous familial hypercholesterolemia

Cell-Replacement Therapies

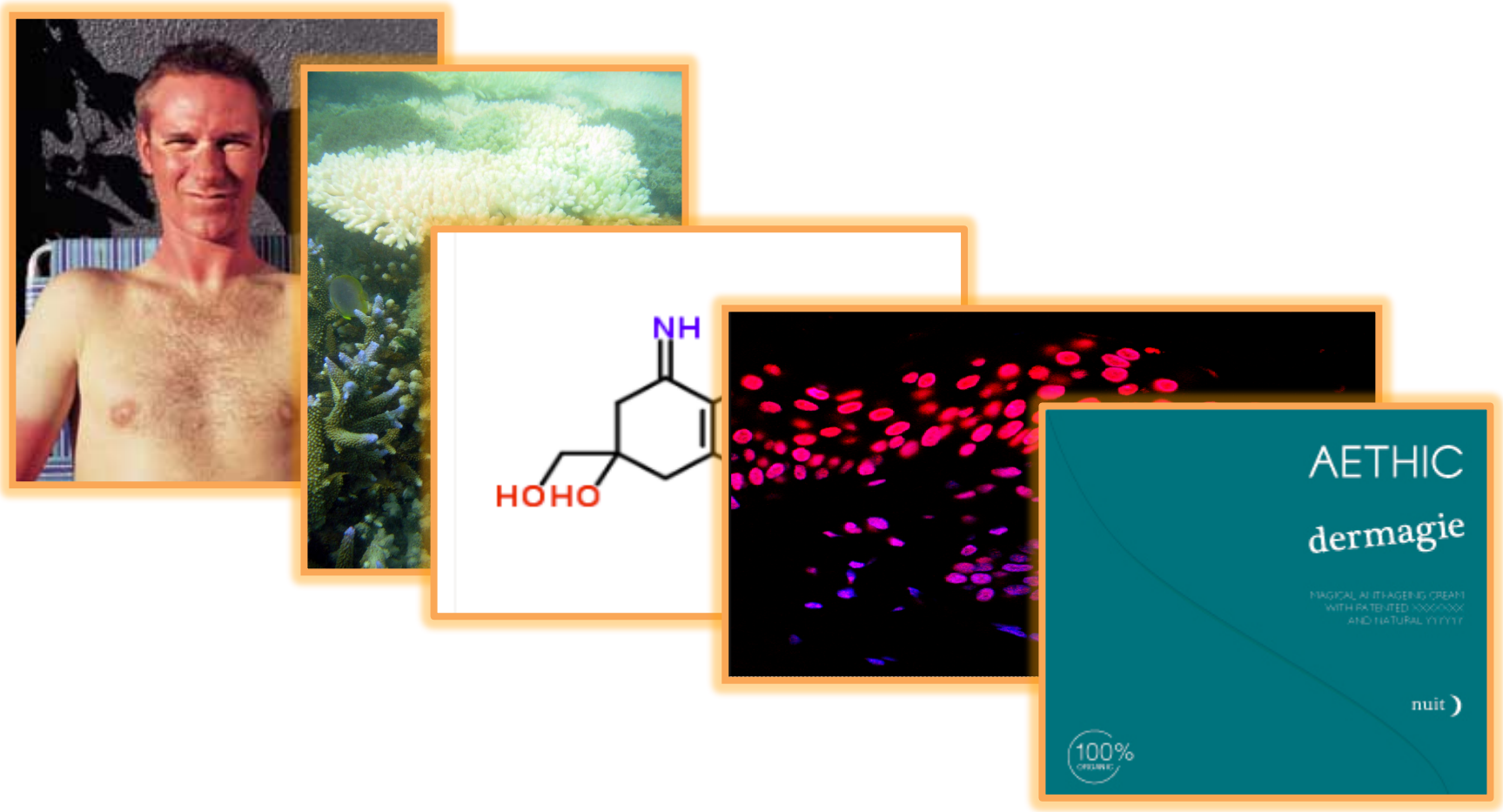


Summary

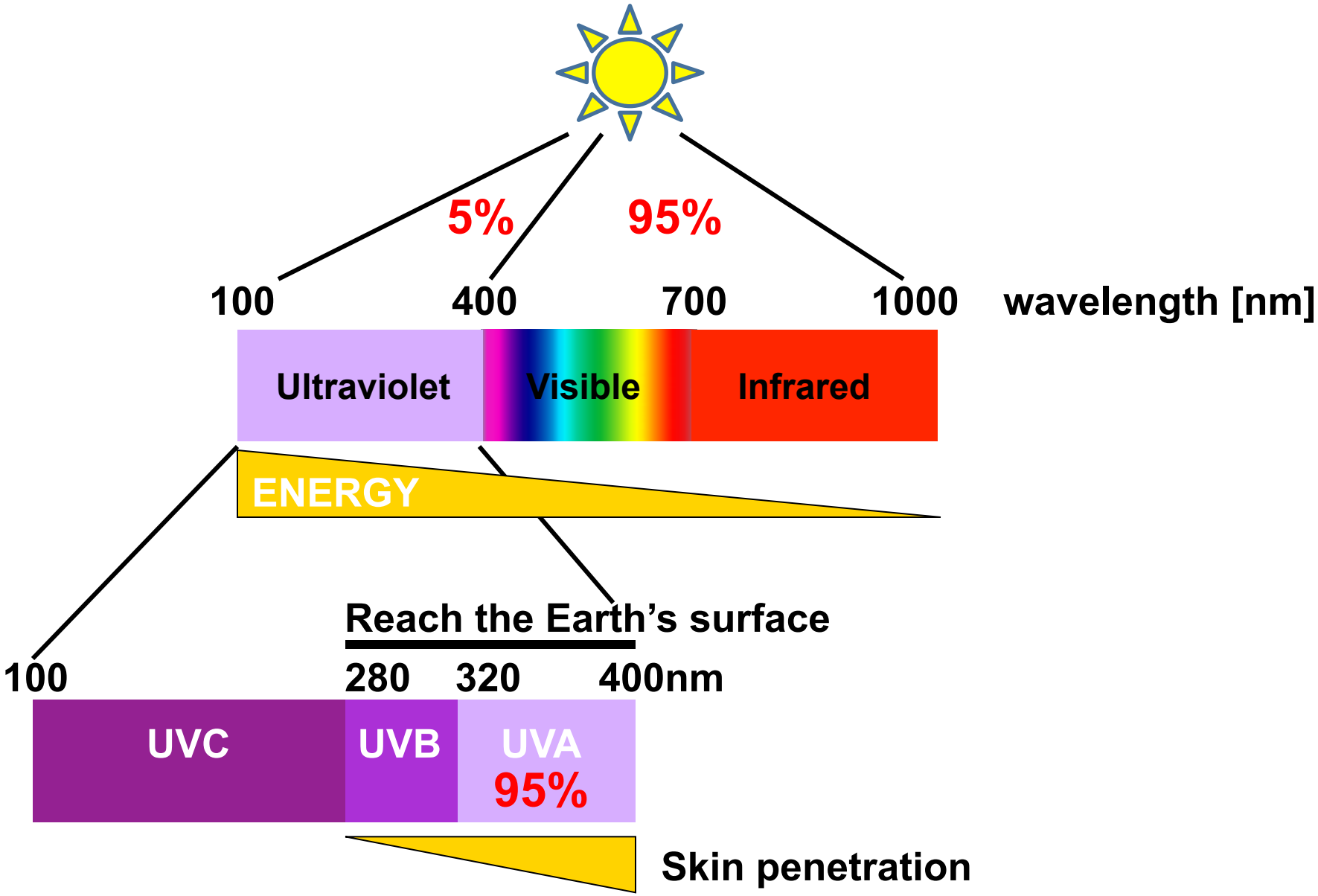
- Therapeutic interventions are important for the health of the individual and the biological and economic health of nations.
- The way drug interventions are delivered by 'Big Pharma' is changing from 'One size fits all' towards 'personalised medicines'.
- The development over the years of large, chemically diverse small-molecule libraries, many already with 'drug-like' properties built into their structure, reinforces the commitment of the industry to this approach.
- Small organic molecule drugs of molecular weight <500 Da are the preferred therapeutic modality of the major pharmaceutical companies for most disease applications but the landscape is now changing and it has been predicted that by 2020 the most important therapies for treating human diseases will be biologicals.

COFFEE!

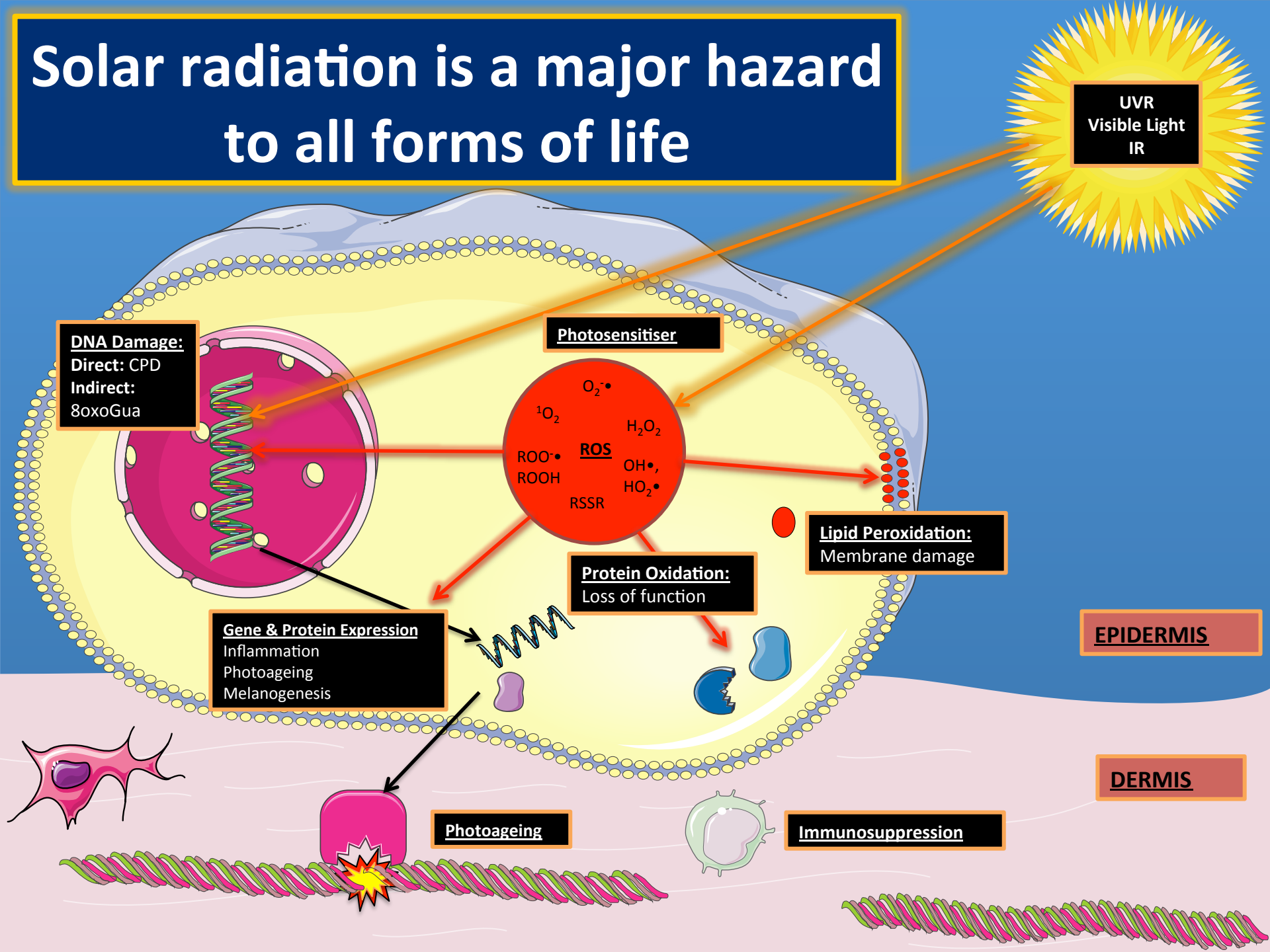
Adventures in Marine Biology: Commercialisation of a Natural Sunscreen & Antioxidant



Solar Ultraviolet Radiation



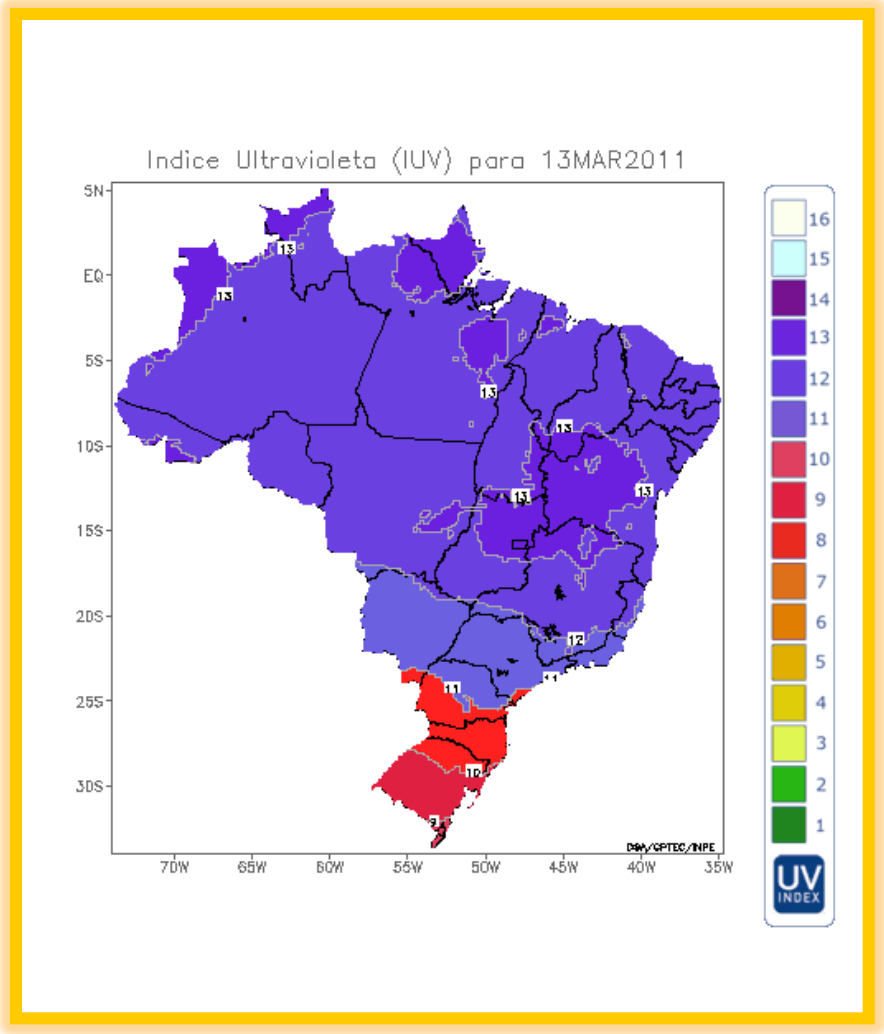
Solar radiation is a major hazard to all forms of life

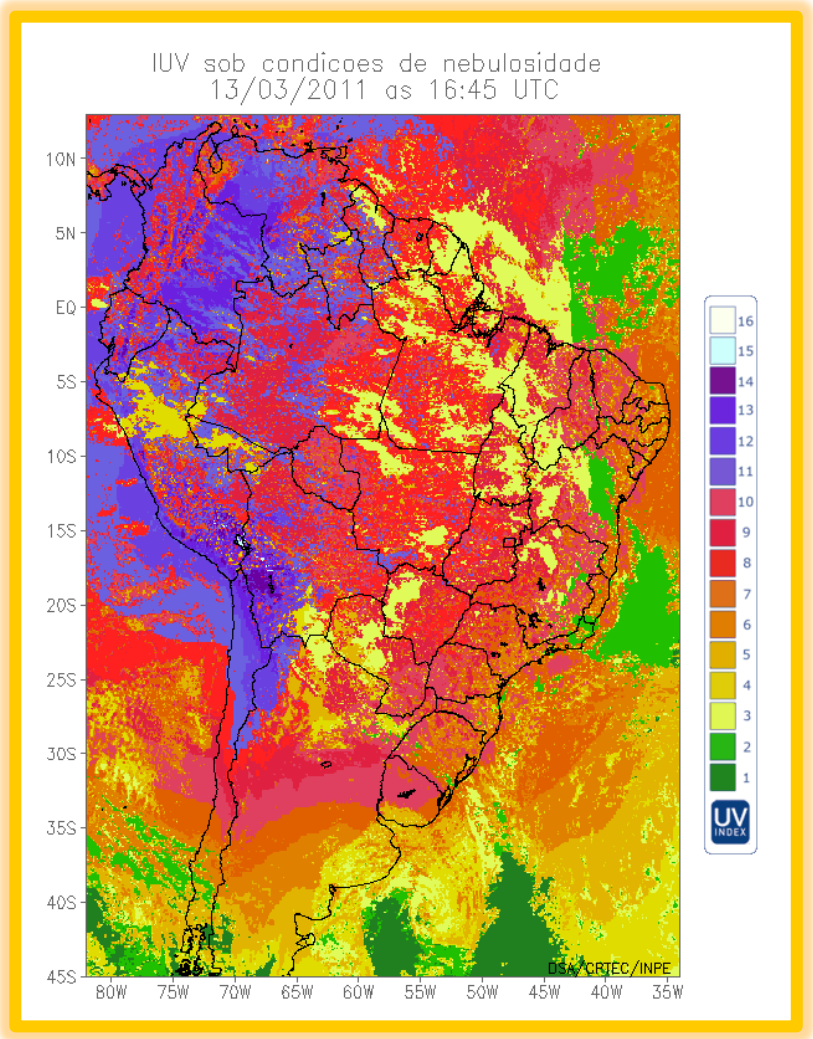


O Índice Ultravioleta (IUV)

O **Índice Ultravioleta** está relacionado à exposição ao Sol de uma pessoa em ambiente aberto. Ele identifica o período do dia quando a exposição aos raios UV é mais intensa. O **IUV** é uma importante ferramenta na educação do público sobre os perigos da exposição excessiva à R-UV e sobre as precauções necessárias para uma exposição segura.

IUV de Norte a Sul do Brasil





Synthetic Sunscreens

Cosmetic/drug formulations containing:

- Inorganic molecules (scatter/reflect/absorb UVR)
- Organic molecules (mostly absorb UVR)

Environmental Issues with Synthetic Sunscreens

Studies have reported that UVR filters:

- cause hormonal changes in fish
- are bioaccumulated in the food chain, with some filters found in birds and marine mammals
- can fuel algal growth (release of inorganic nutrients from formulations)

TESTIMONIES DUE 3/20 10AM
HEARING SET 3/21 10AM

European Chemicals Agency CoRAP List Filters

8 of 16 frequently uses filters on CoRAP List:

1. Butylmethoxydibenzoylmethane - vPvB
2. Octocrylene - vPvB
3. Ethylhexyl Methoxycinnamate – ED
4. TiO2 – vPvB, CMR, RS
5. ZnO – Nano, vPvB
6. Benzophenone-3 - ED
7. Isoamyl p-Methoxycinnamate - ED
8. Diethyl Butamido Triazone - vPvB

vPvB = very persistent, very bioaccumilative
ED = Endocrine disruptor
RS = Respiratory sensitizer
CMR = carcinogenic, mutagenic, reprotoxic
Nano = Concerns with nanoform

Marine Biology in London?

The River Thames?...

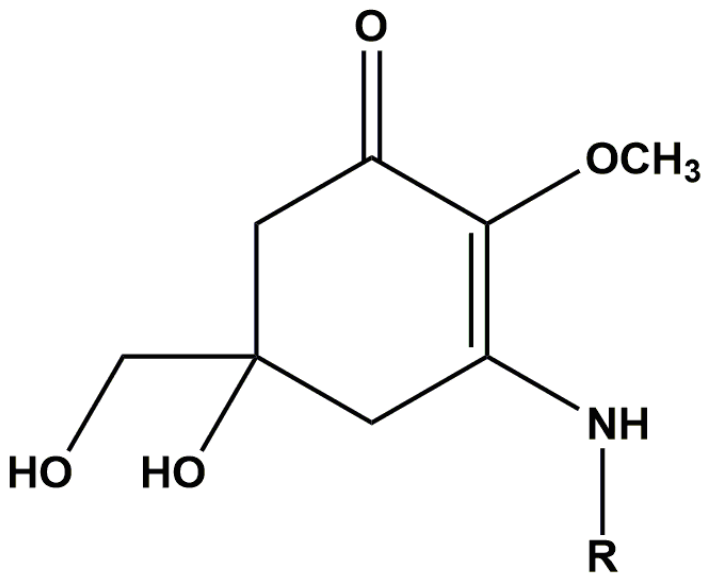
...or the Great Barrier Reef ?

Why don’t corals get sunburnt?

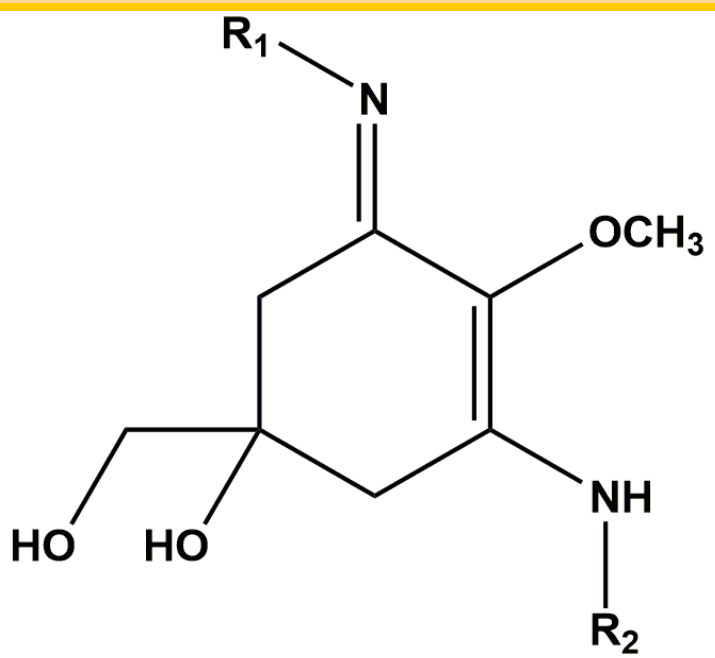
They make their own sunscreen

AUSTRALIAN INSTITUTE OF MARINE SCIENCE

Mycosporines & Mycosporine-like Amino Acids (MAAs)



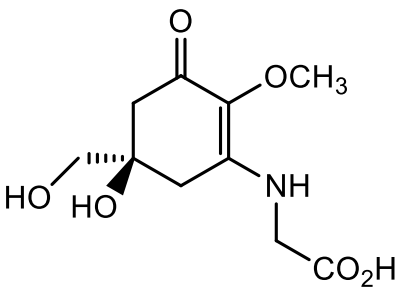
Mycosporine



Mycosporine-like Amino Acid

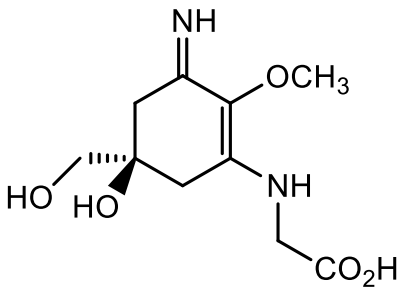
Commonly produced by marine algae & seaweeds and are found in tissues of some marine animals by dietary accumulation

Typical MAAs produced in coral-algal symbioses



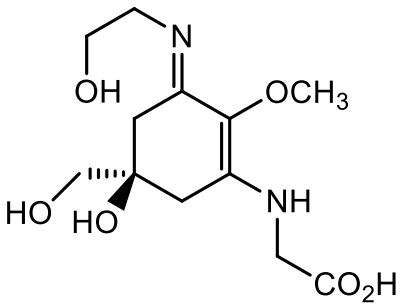
Mycosporine-Gly

λ_{max} = 310 nm



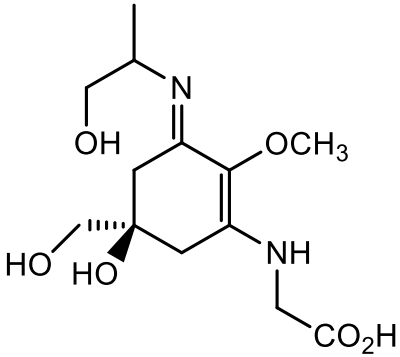
Palythine

λ_{max} = 320 nm



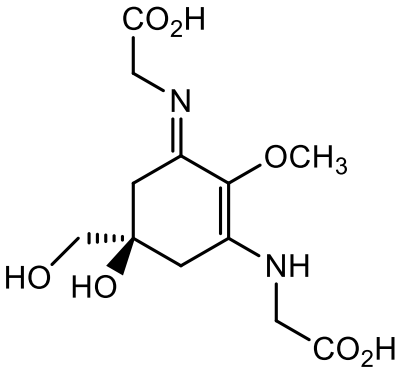
Asterina-330

λ_{max} = 330 nm



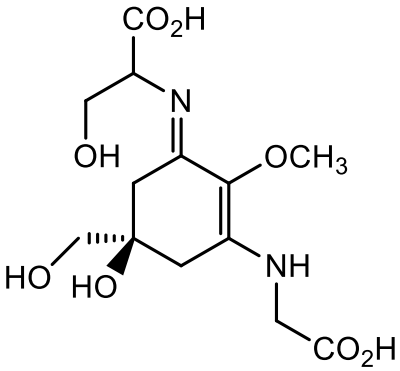
Palythinol

λ_{max} = 332 nm



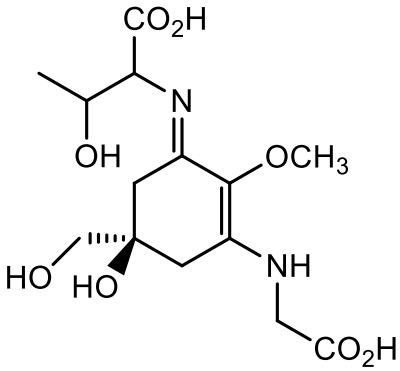
Mycosporine-2Gly

λ_{max} = 334 nm



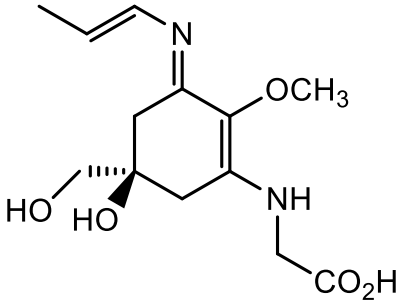
Shinorine

λ_{max} = 334 nm



Porphyra-334

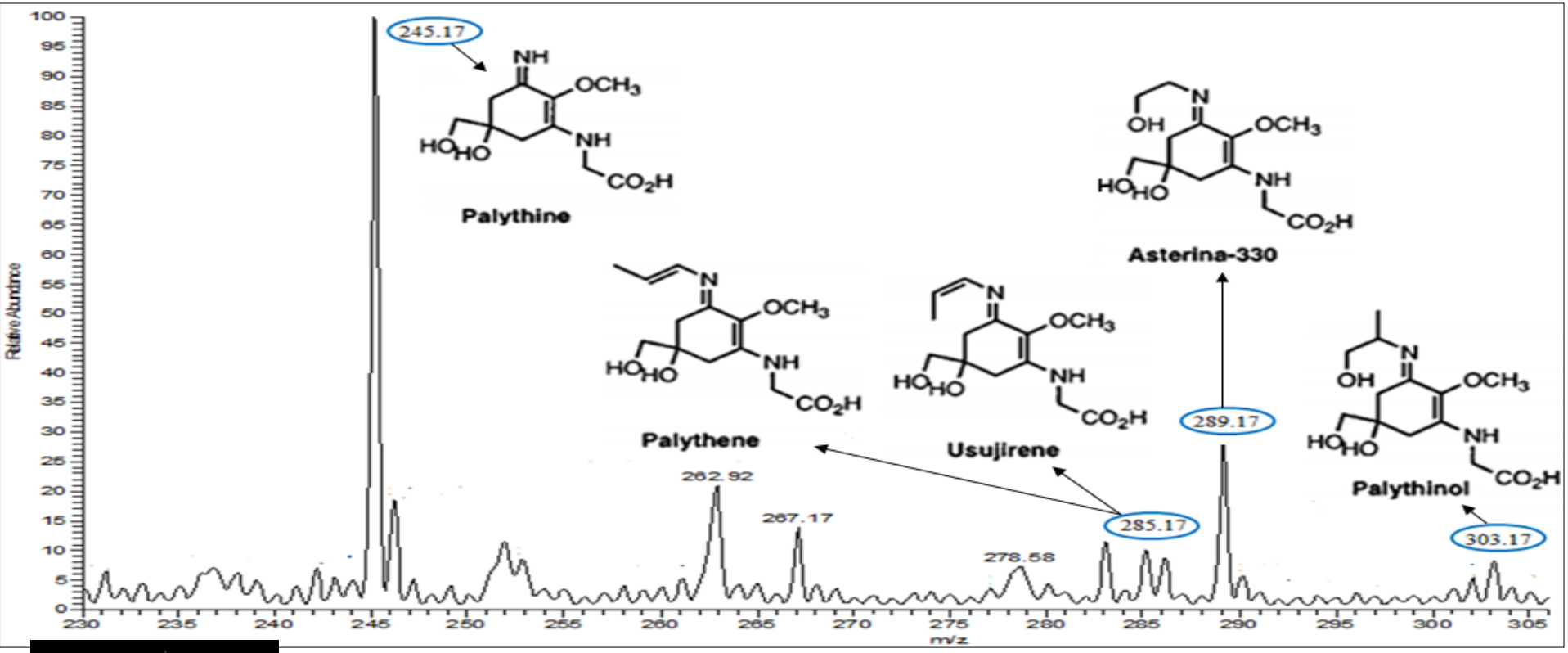
λ_{max} = 334 nm

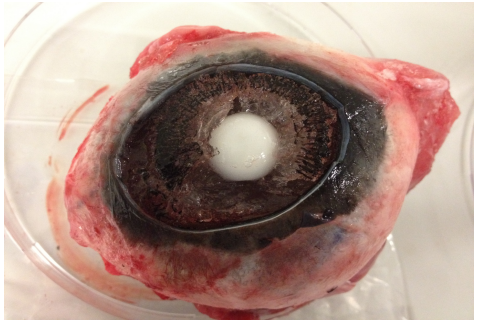


Palythene

λ_{max} = 360 nm

Natural Catch Fish From Tropical & Temperate Waters Contain the Same MAAs in Ocular Lens, Skin & Roe



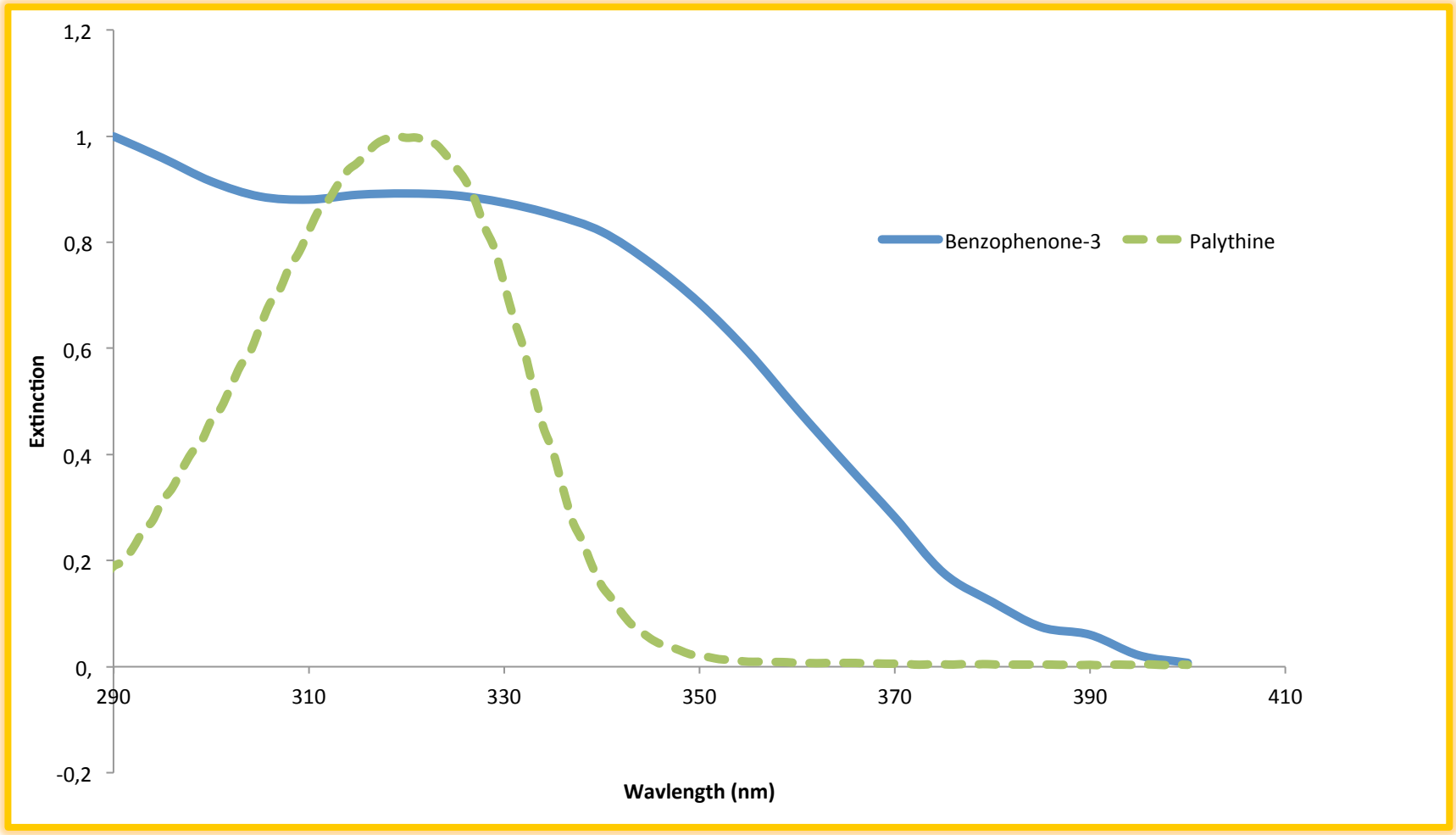


Photoprotection studies (*in vitro*) using palythine as a model MAA

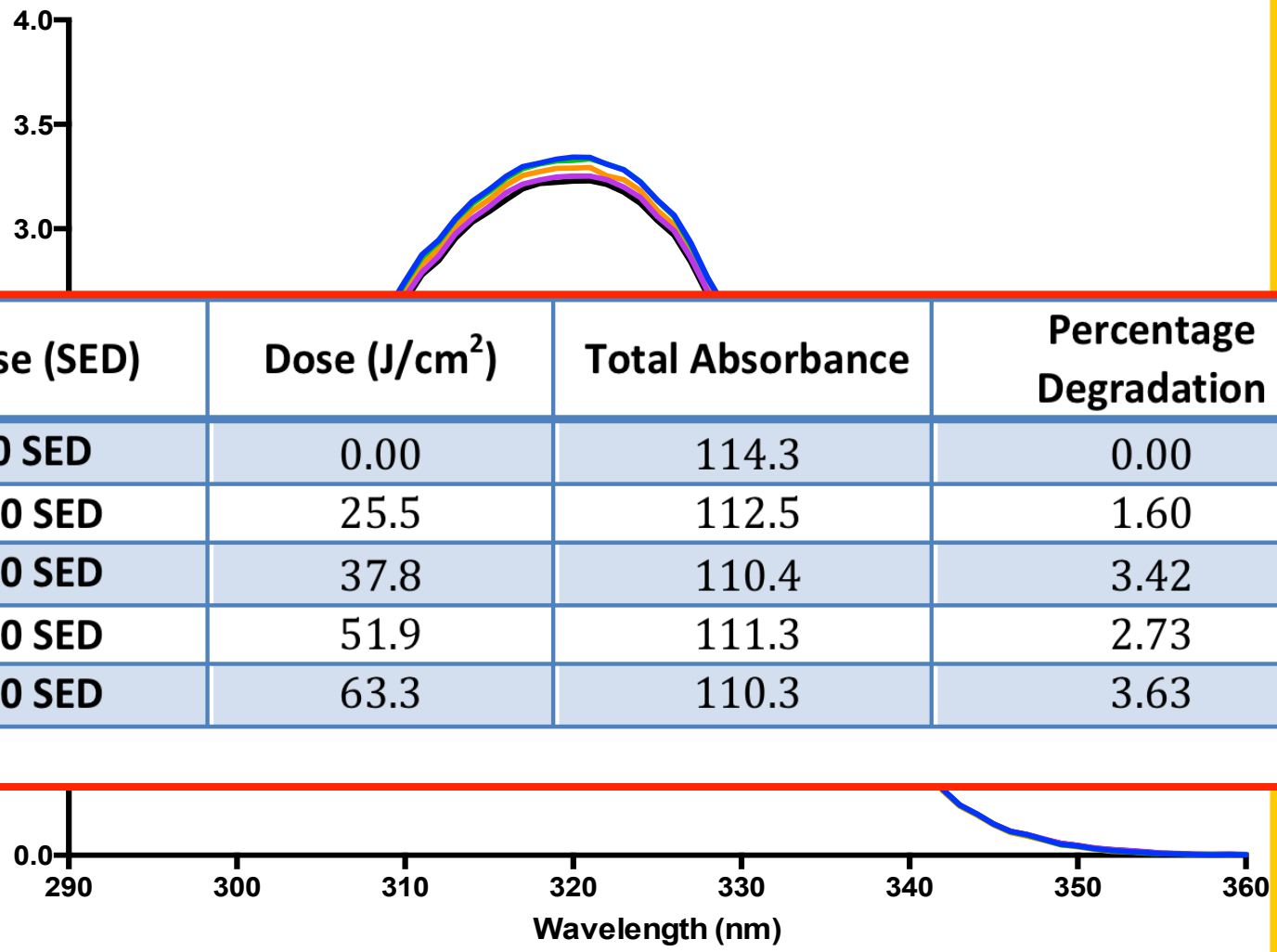
Source: edible South East Asian seaweed *Chondrus yendoi* – Japanese "Buddha's ear"

- Solar range & photostability
- Biological assays
  - Cell survival
  - DNA damage (direct and oxidative)
  - Induction of ROS
  - Gene expression (adverse UVR effects)
- Chemical assays for anti-oxidant effect

Absorption spectrum of palythine in comparison with oxybenzone

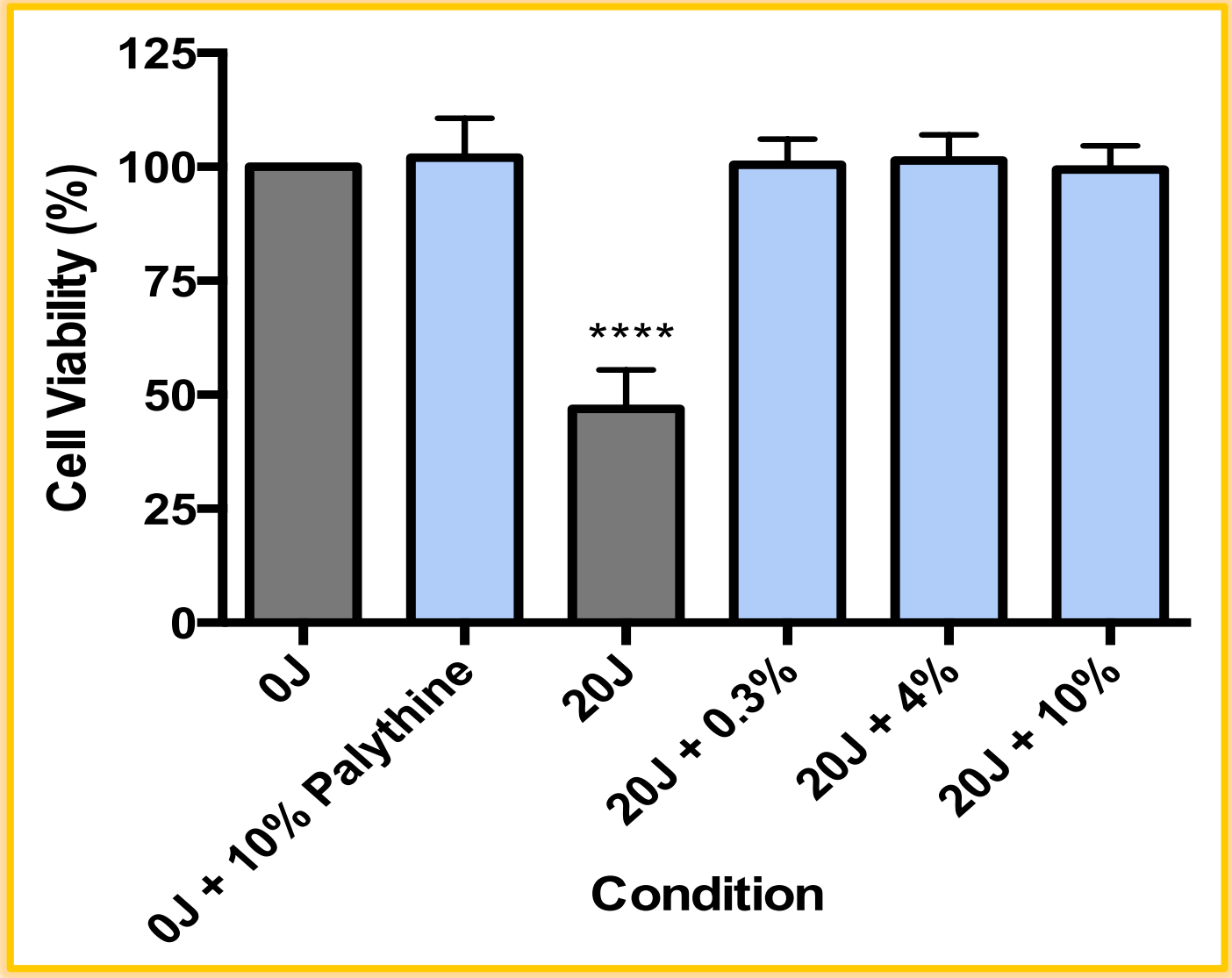


Palythine photostability *in vitro*

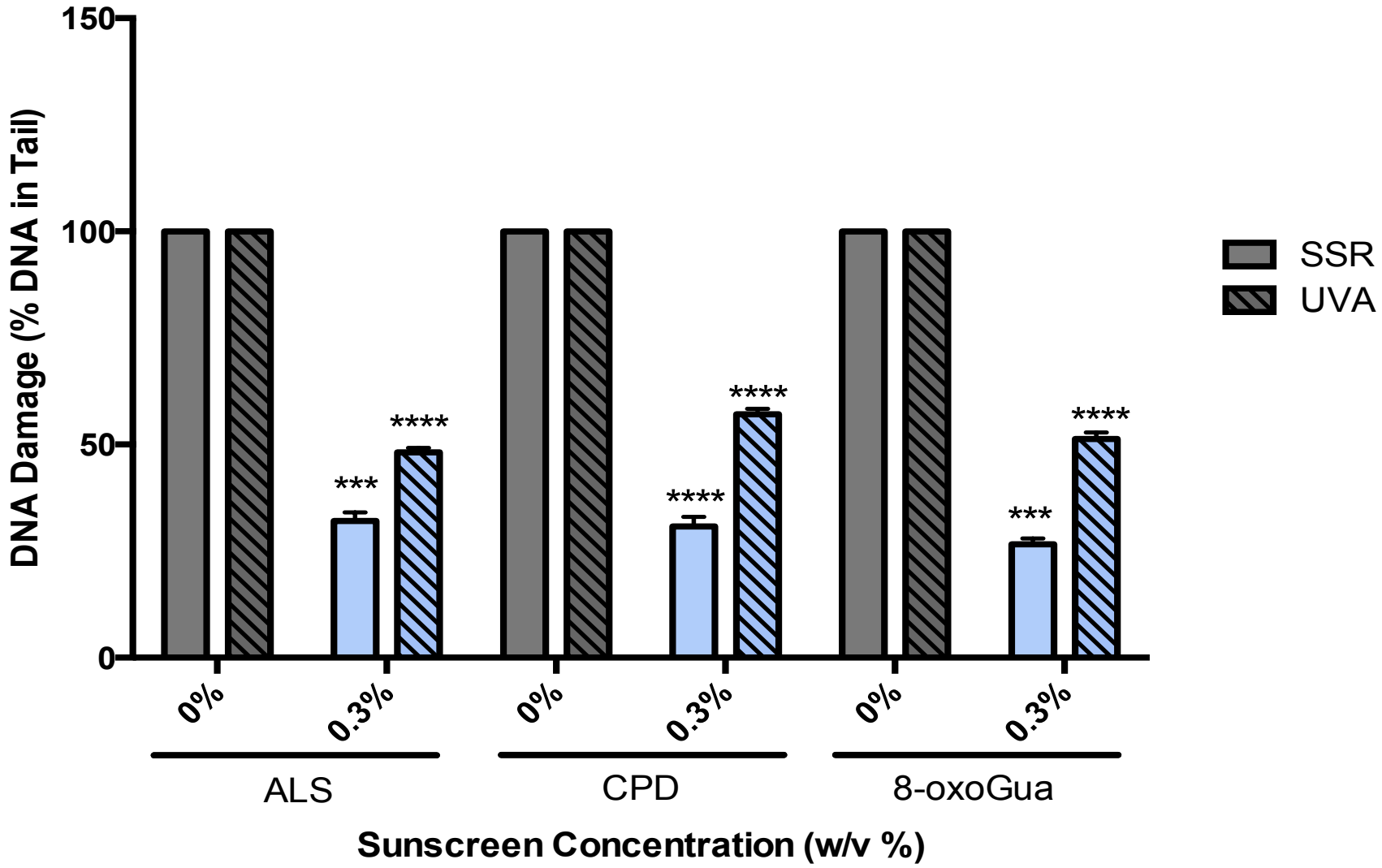


Dose (SED)	Dose (J/cm^2)	Total Absorbance	Percentage Degradation
0 SED	0.00	114.3	0.00
20 SED	25.5	112.5	1.60
30 SED	37.8	110.4	3.42
40 SED	51.9	111.3	2.73
50 SED	63.3	110.3	3.63

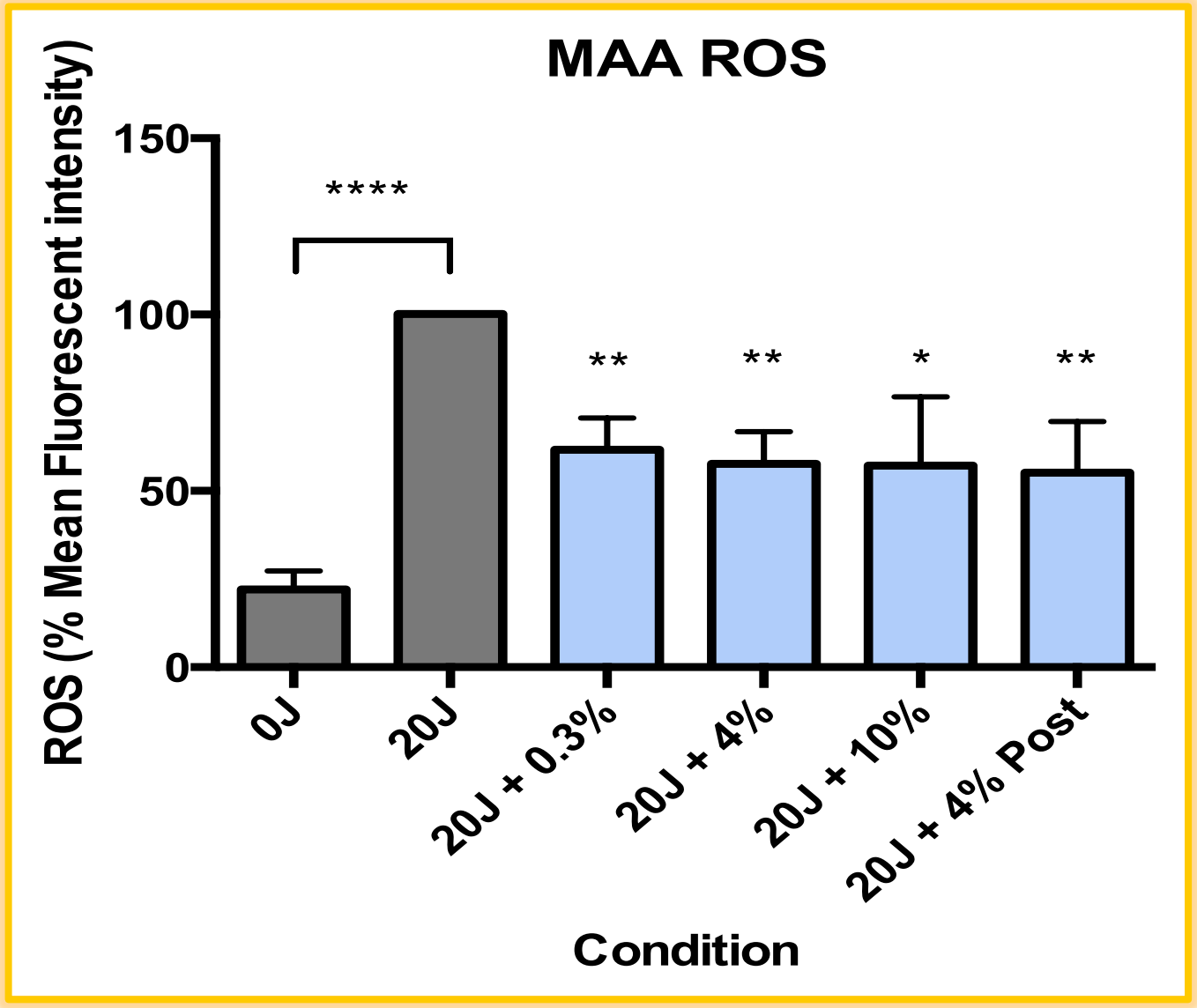
Cell Viability



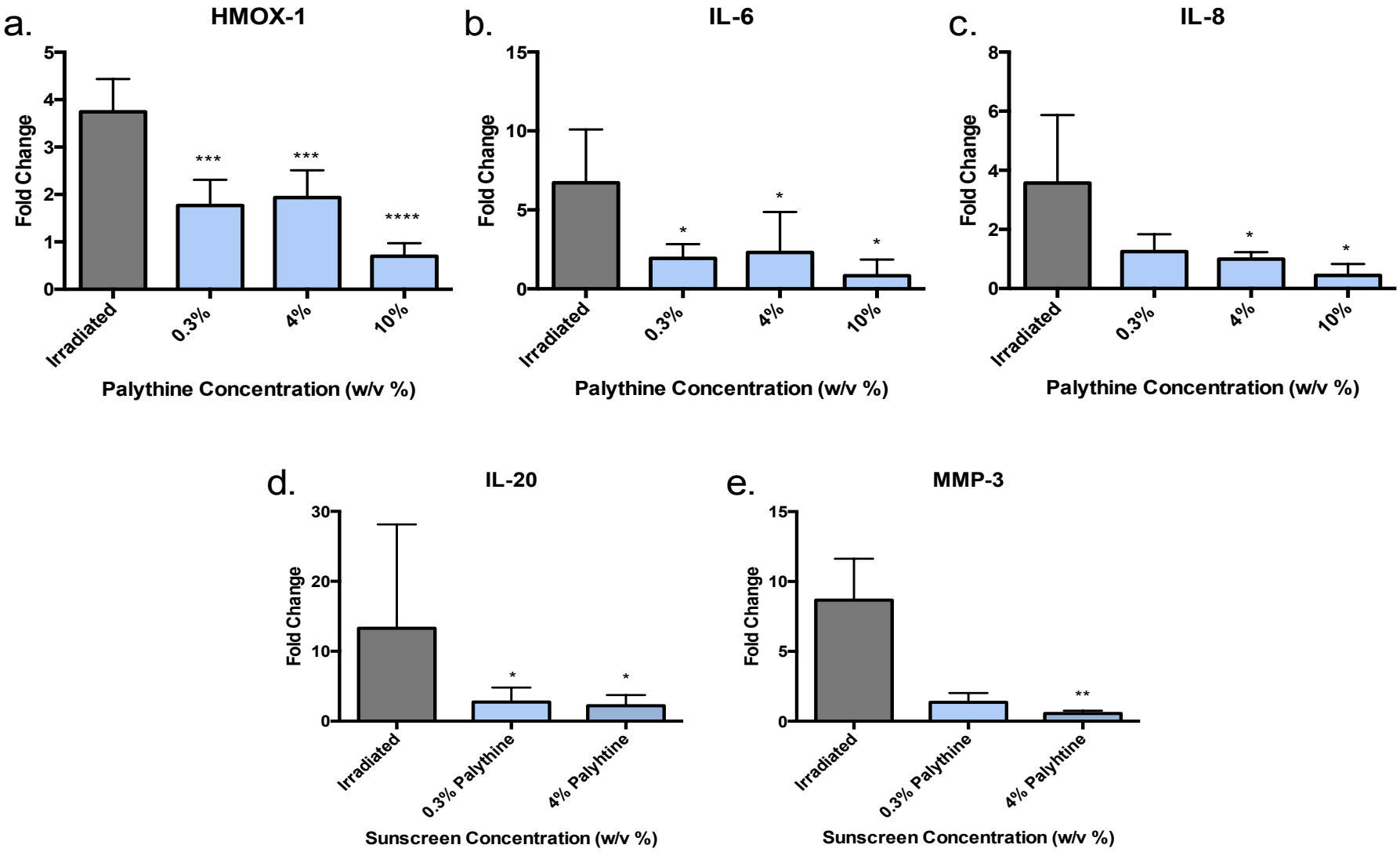
DNA Damage


150
100
50
0
DNA Damage (% DNA in Tail)
***
****
****
****
***
****
0%
0.3%
0%
0.3%
0%
0.3%
ALS
CPD
8-oxoGua
Sunscreen Concentration (w/v %)
SSR
UVA

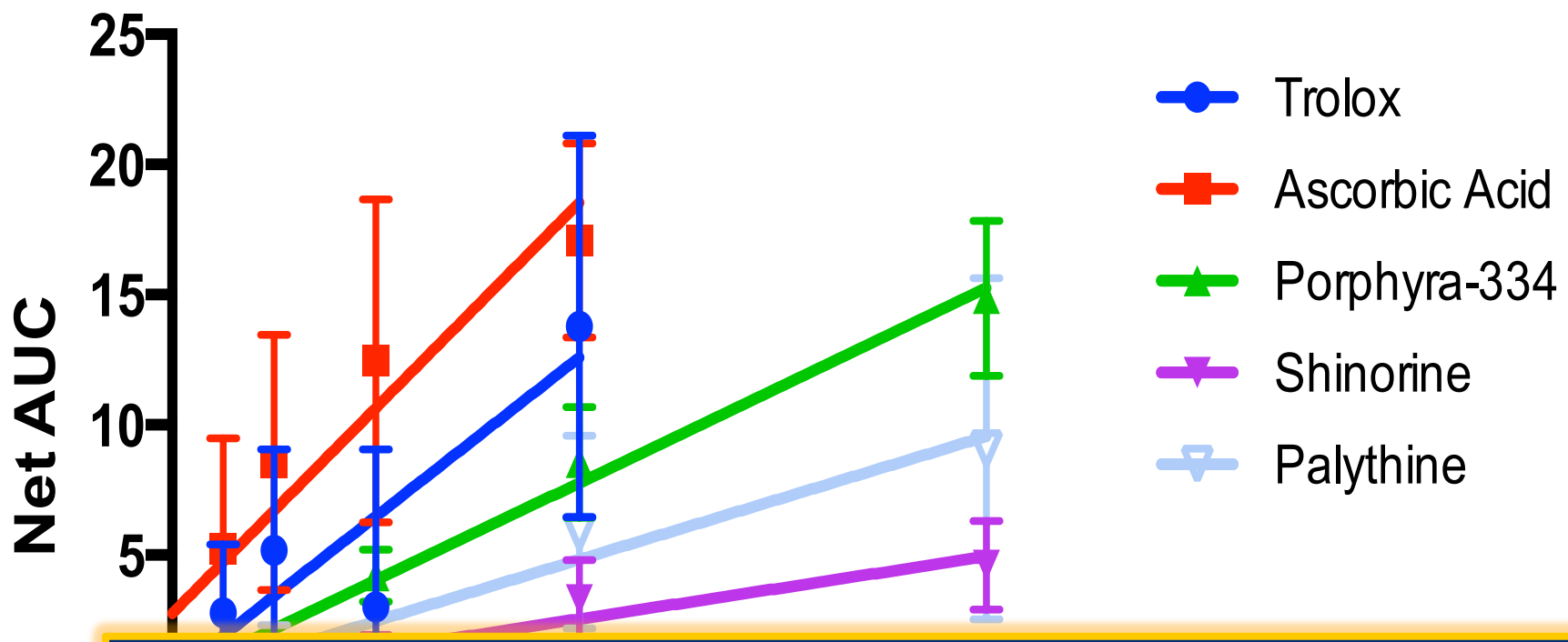
Induction of ROS



Gene Expression



ORAC Assay
(radical quenching by hydrogen atom transfer)



No significant radical quenching by electron transfer (DPPH Assay)

Requirements of an Effective Sunscreen

- Significant absorption ✓
- Sufficient photostability ✓
- Non-toxic ✓
- High solubility ✓
- Colourless ✓
- Prevent UV induc

PCT/GB2016/052227
Priority date 23/7/15
Filing date 22/7/16
Publication date 26/1/17

AETHIC

dermagíe

VEGAN ORGANIC ANTI-AGEING CREAM

WITH photamin®

UVA/UVB LIGHT FILTER AND ANTI-OXIDANT
EXTRACTED DIRECTLY FROM EDIBLE SEAWEED

Summary

- UVR exposure initiates molecular changes in the skin that can lead to cancer and photoageing.
- Sunscreens can prevent molecular photodamage but there are environmental, health and perception concerns.
- MAA are natural, biocompatible compounds that are extremely effective in reducing UVR induced molecular
- MAA have
over synth
- A better ba

SeaYield
Specialist Seaweed Products