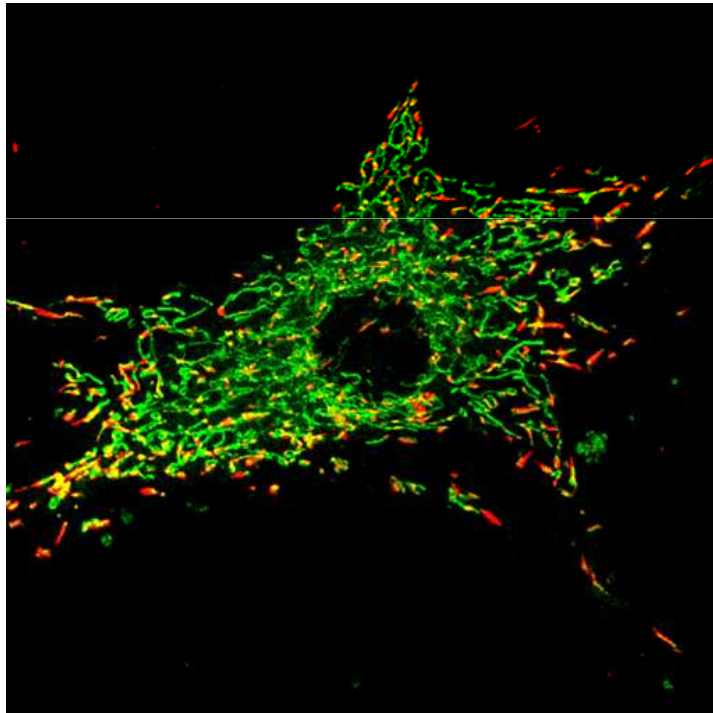


Molecular by-pass therapy for mitochondrial dysfunction

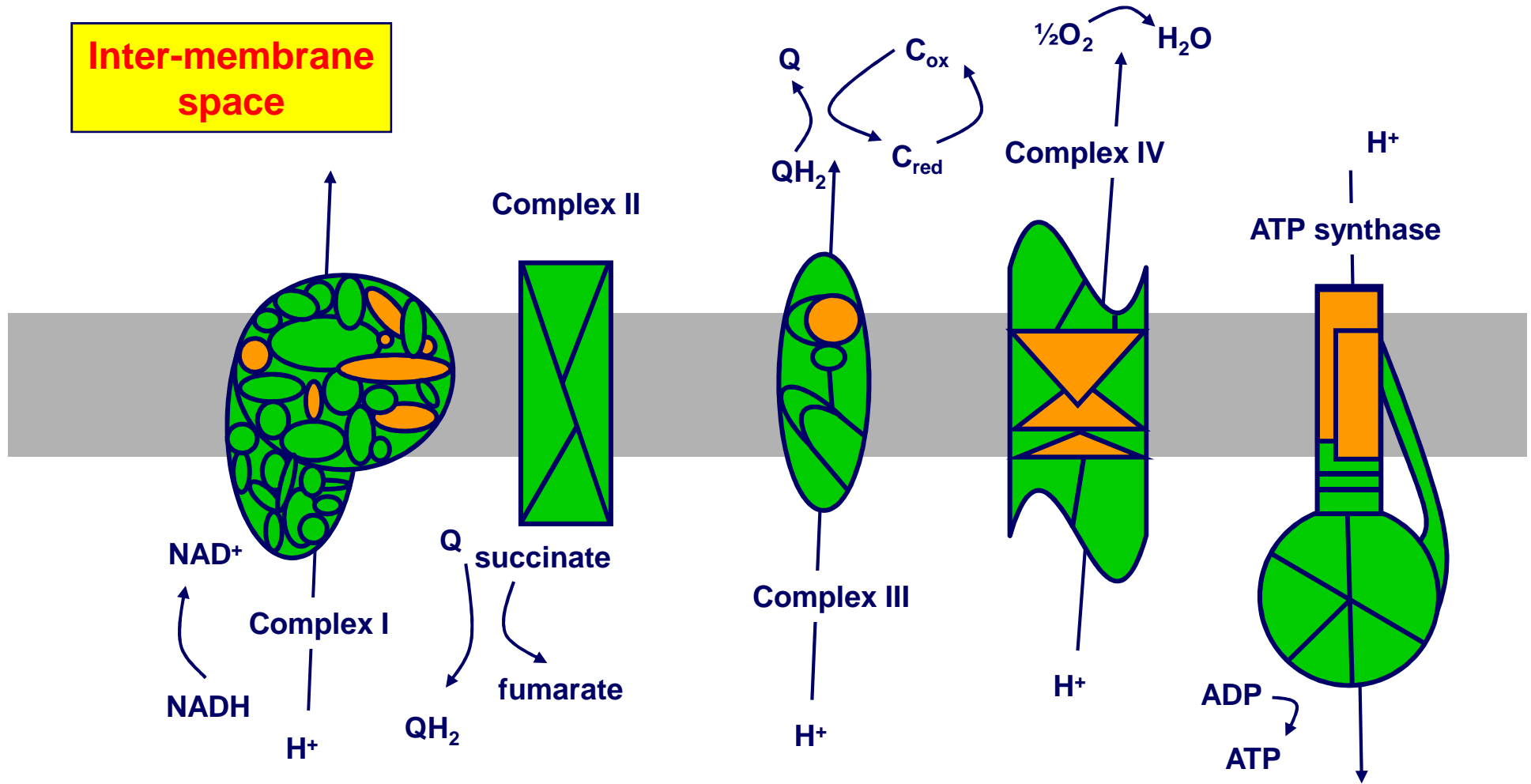
Howy Jacobs

IMT Tampere

Mitochondria are the power stations of our cells



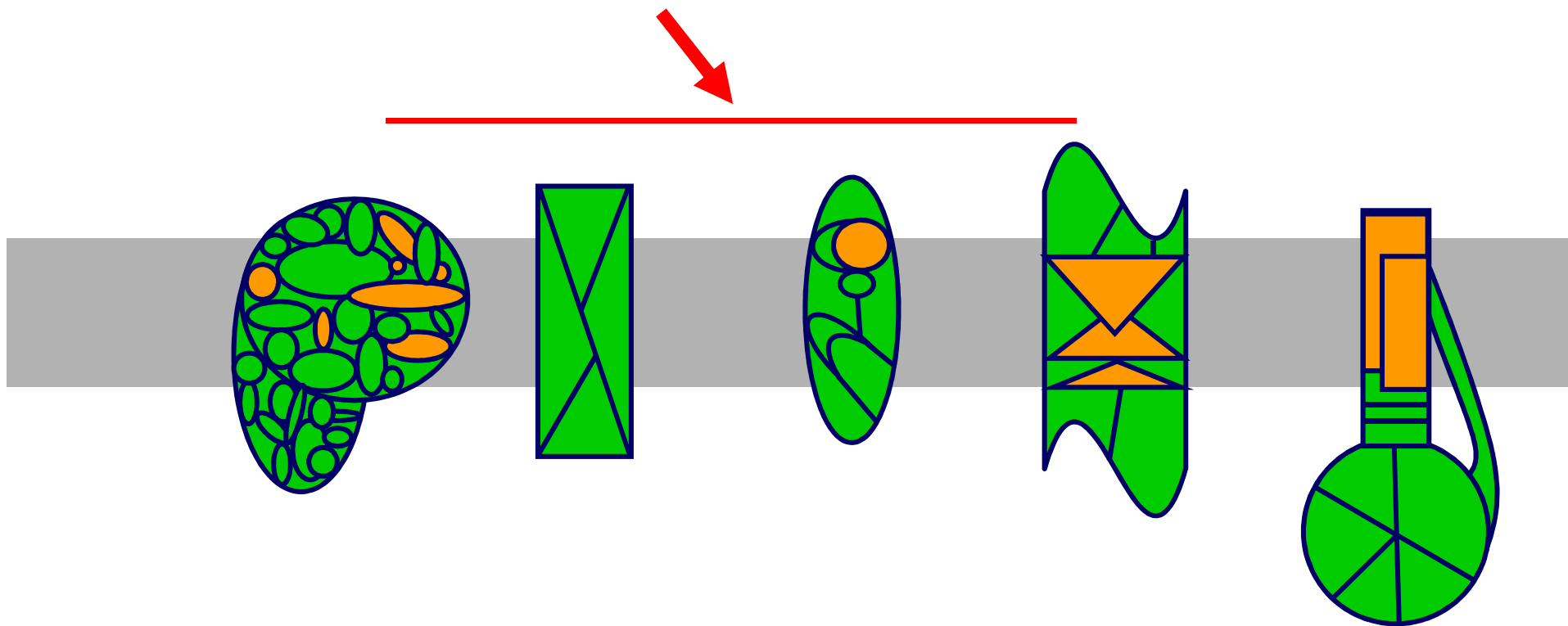
Inter-membrane space



The mt OXPHOS system

Matrix

A series of waterfalls which drive the turbine



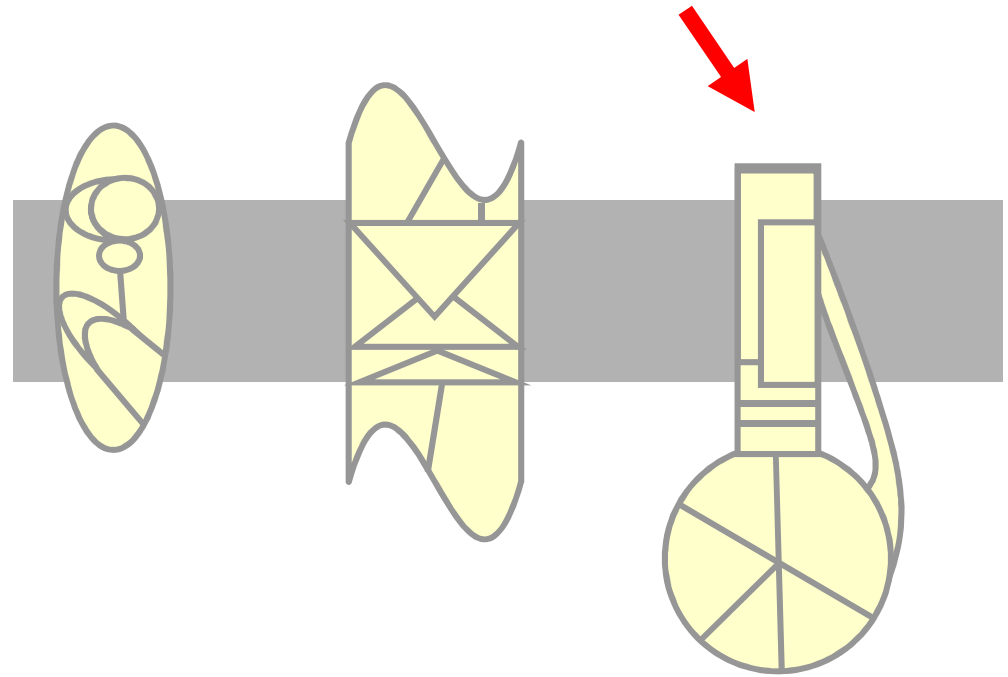
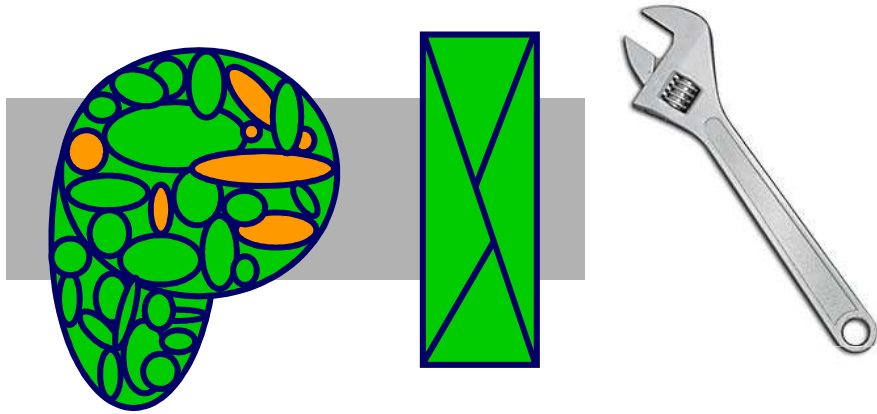
The molecular turbine that generates the electricity

If a pipe conveying water to the turbines gets blocked....

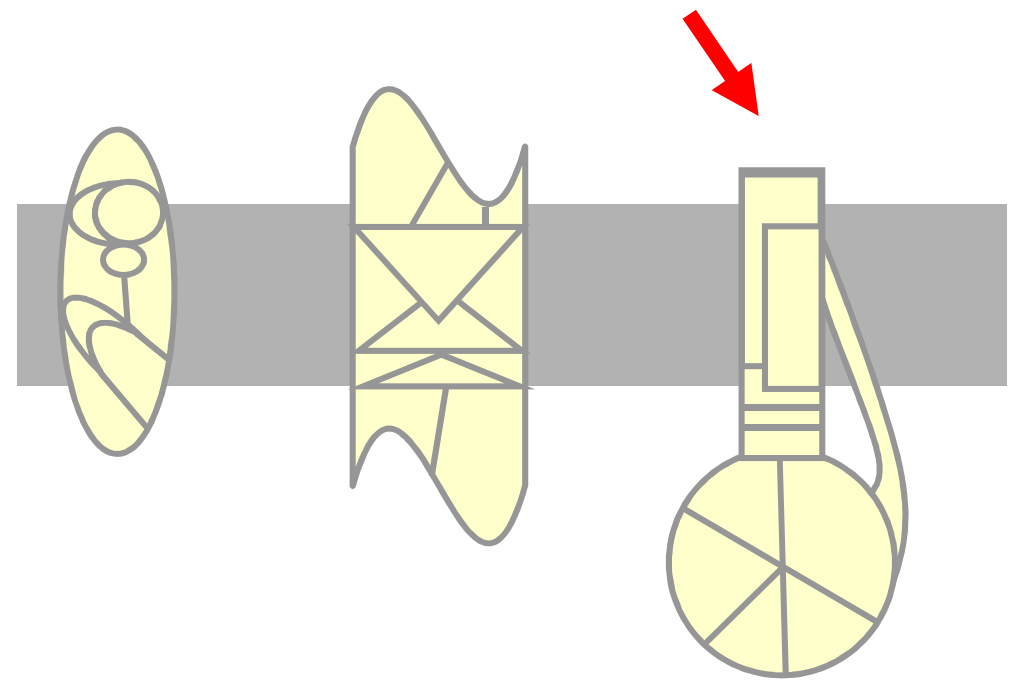
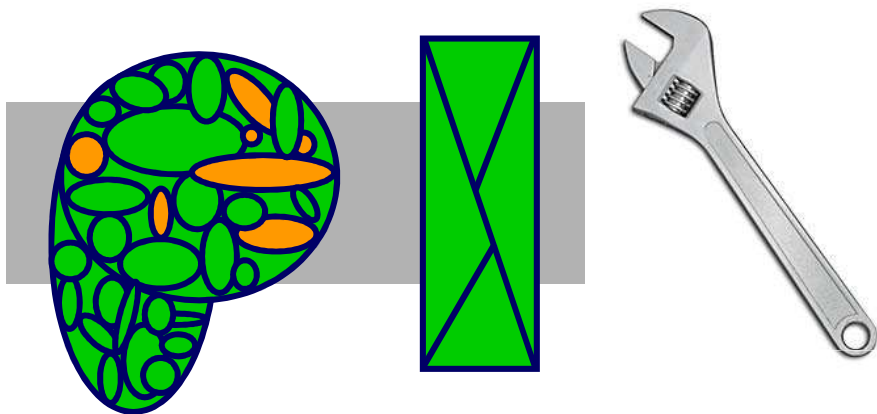


... the whole system fails

Power to the turbine is lost

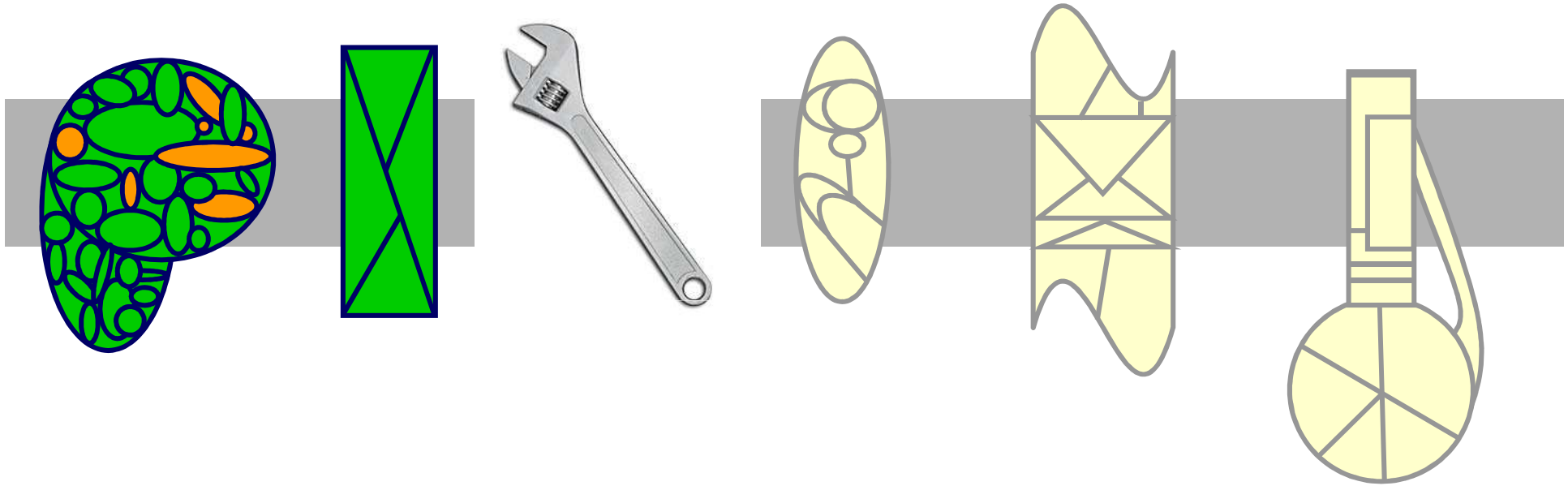


Power to the turbine is lost



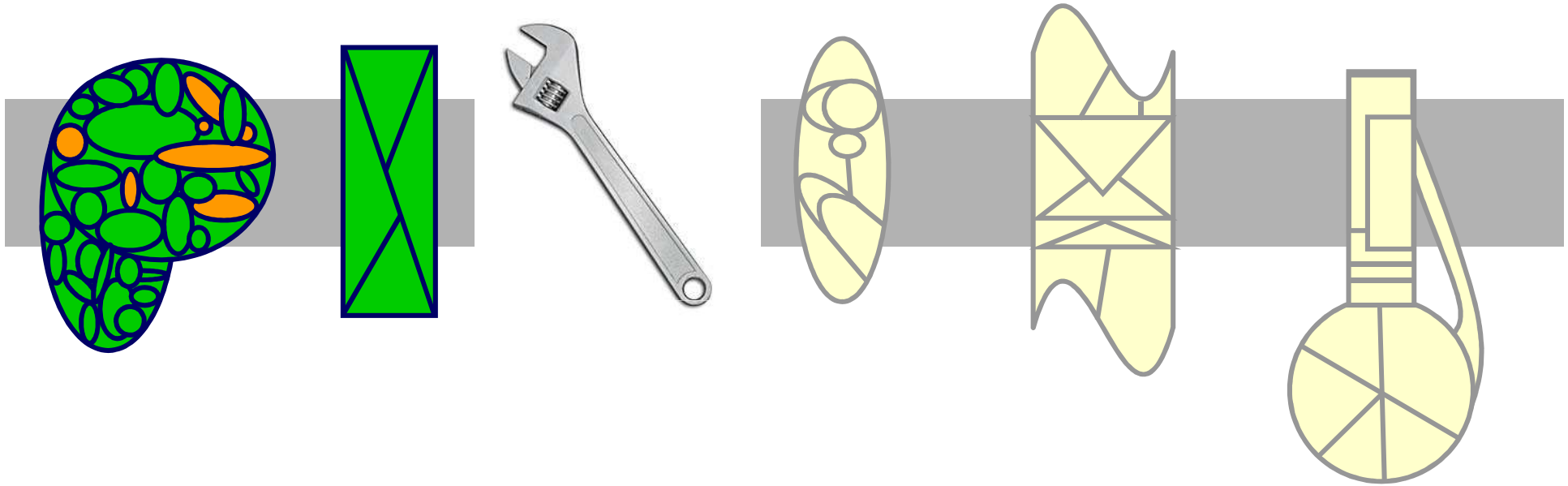
Pressure in the blocked pipe results in leaks and catastrophic failure

When this happens in mitochondria, devastating diseases result



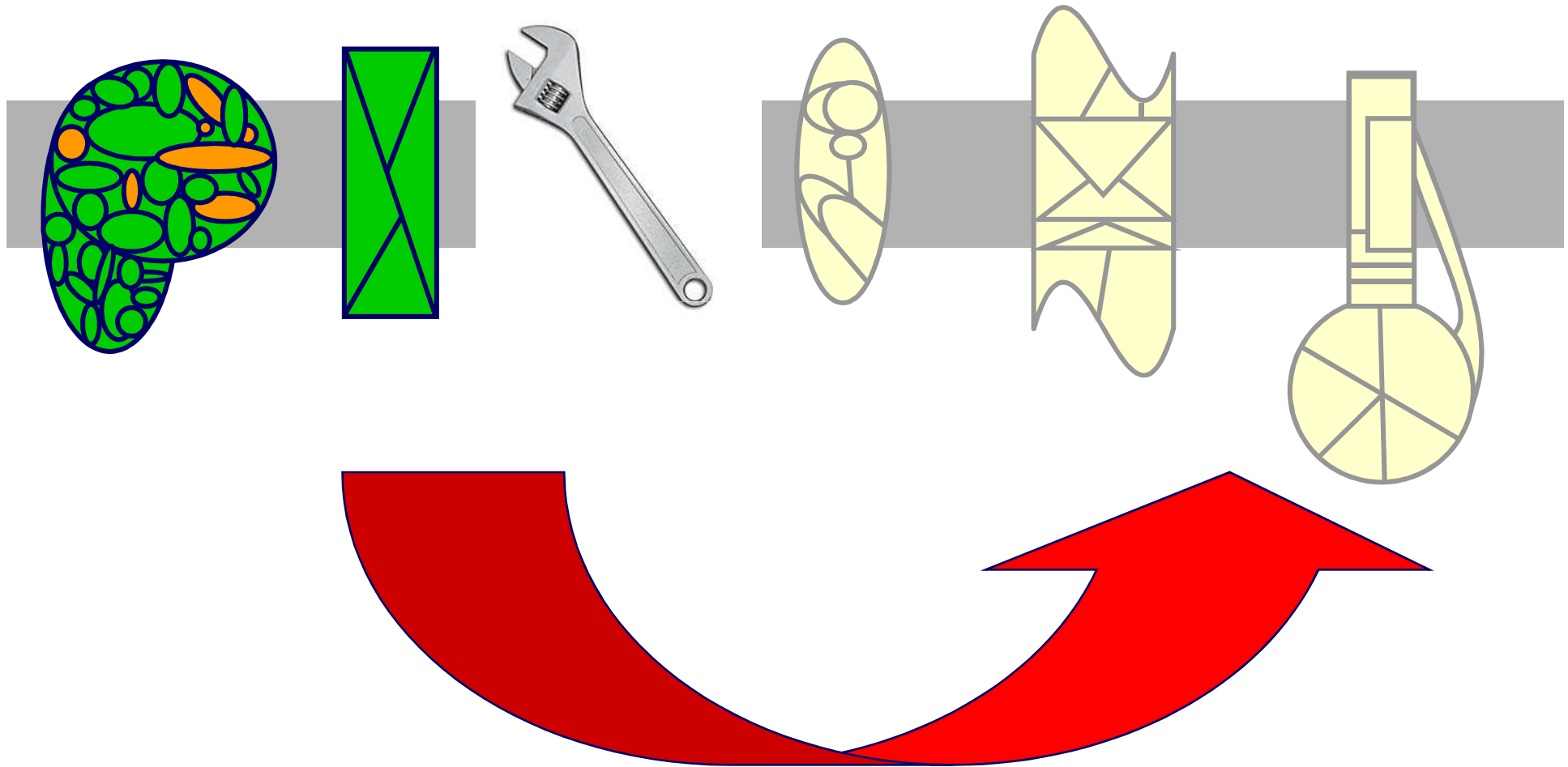
- **failure of cellular energy supply**
- **leakage of toxic by-products (oxygen radicals)**
- **cell death**

When this happens in mitochondria, devastating diseases result

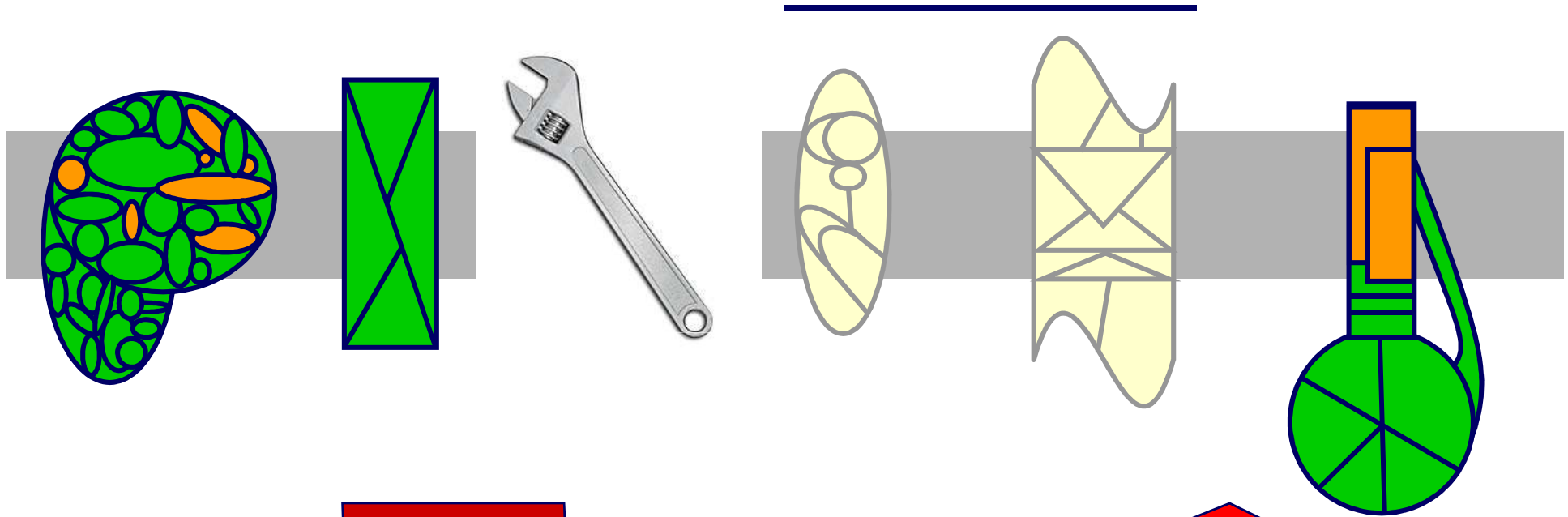


- fatal infantile diseases, e.g. Leigh syndrome
- Parkinson's disease
- tissue damage following stroke or heart attack
- diabetes, deafness, epilepsy.....

Our strategy - to relieve blockages by a by-pass enzyme

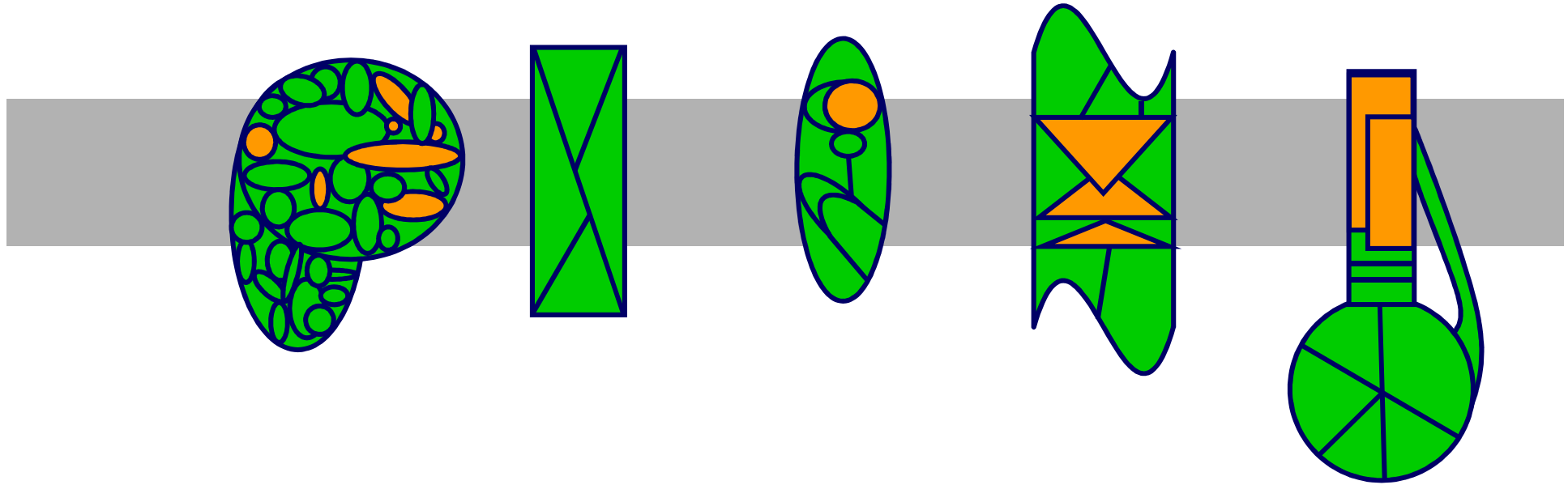


Part of the water power is still missing....

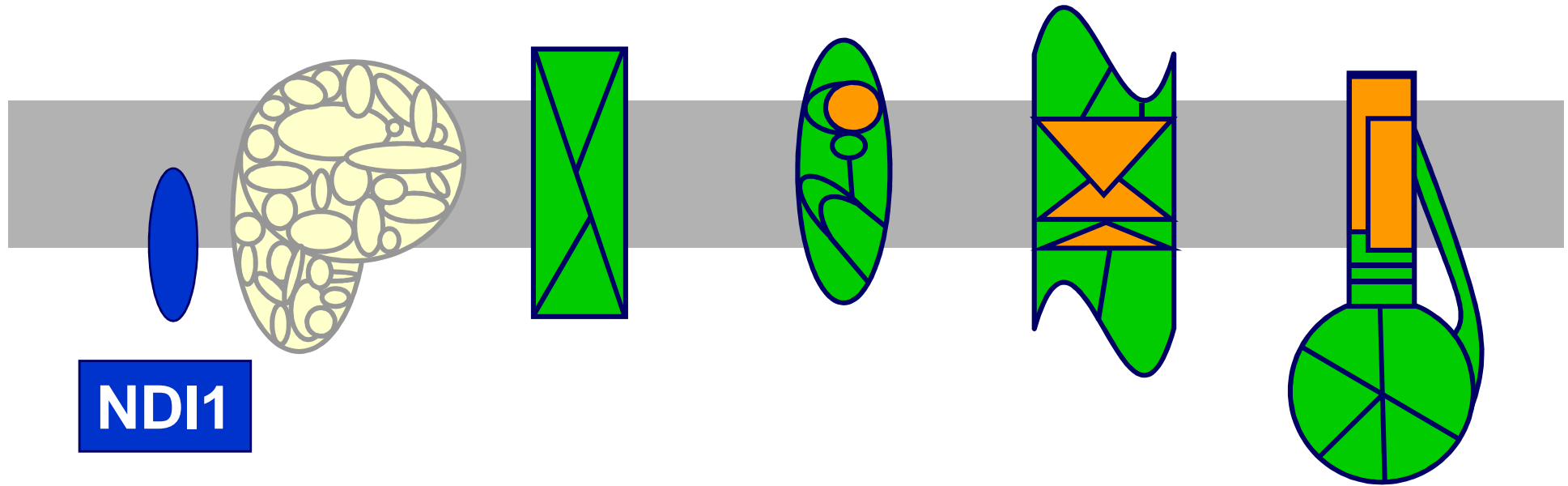


...but the turbine is now working again and there are no leaks

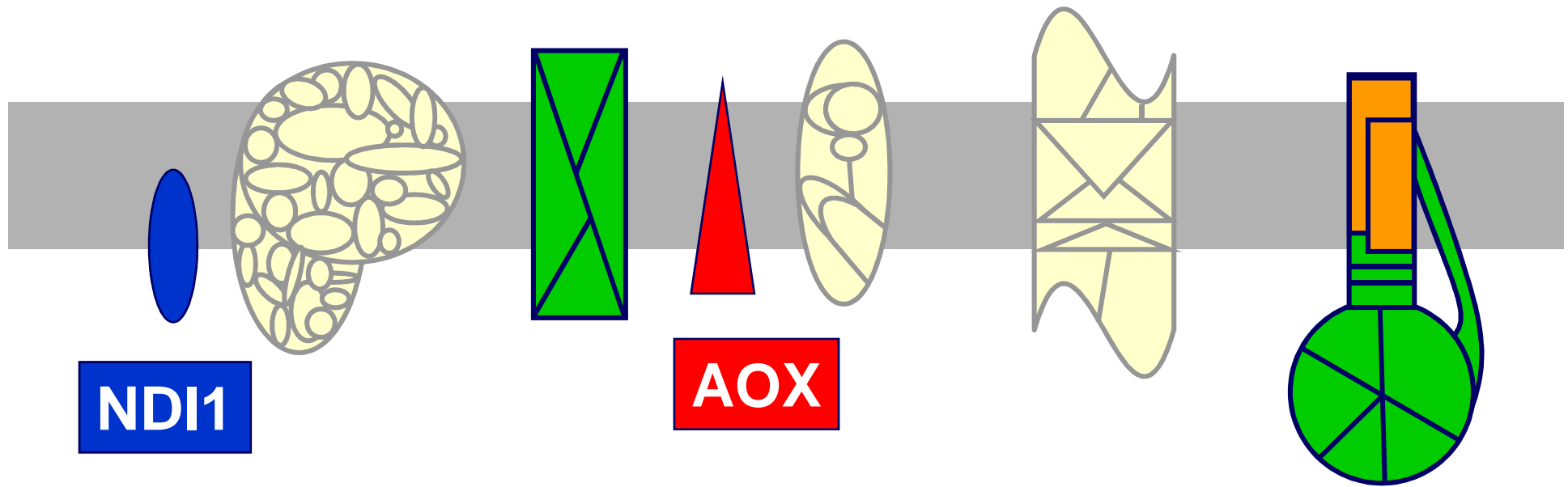
A single by-pass protein can replace any, or all, of dozens of others



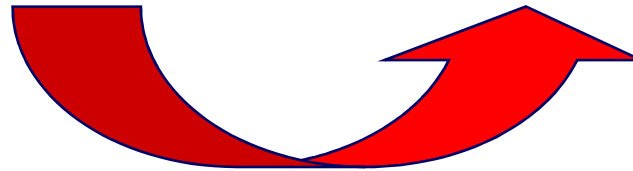
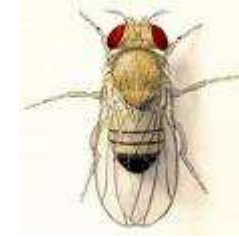
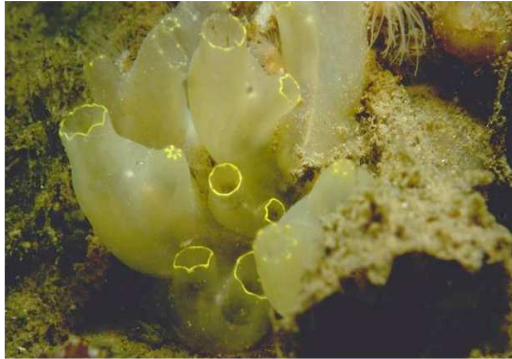
A single by-pass protein can replace any, or all, of dozens of others



A single by-pass protein can replace any, or all, of dozens of others



The Project



Genes for mitochondrial by-pass enzymes from 'lower' organisms

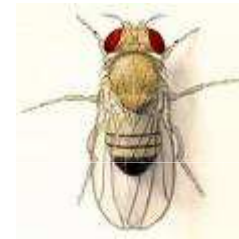
- effects on normal development and physiology
- resistance to toxins
- curing genetic diseases of mitochondria
- customizing the by-pass enzymes for therapeutic use

The Alternative Oxidase

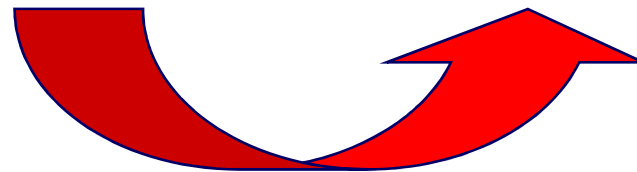


from the sea squirt

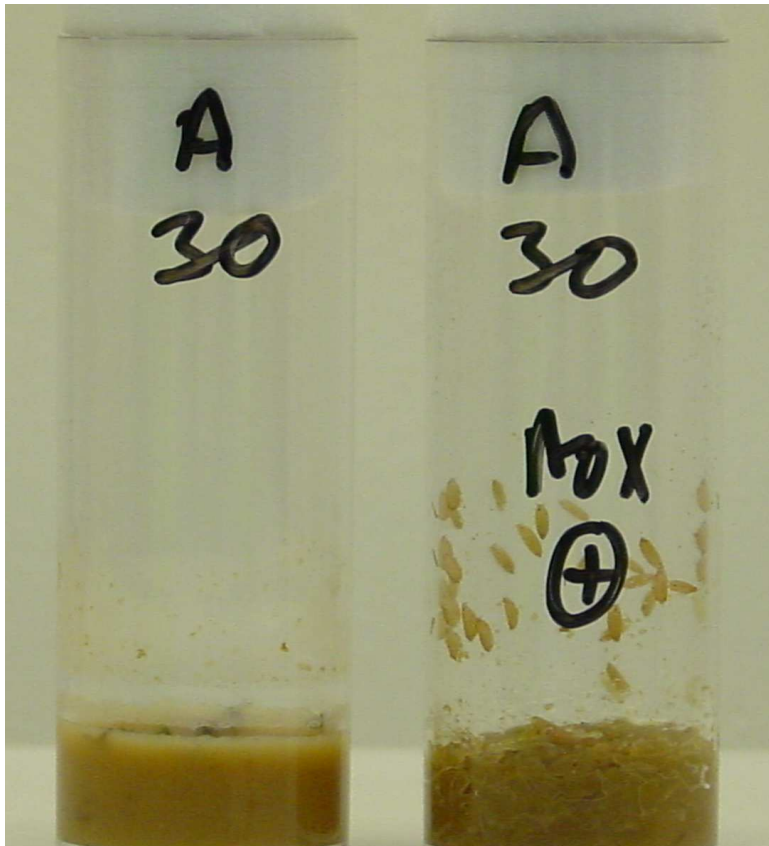
to the fruit fly



AOX

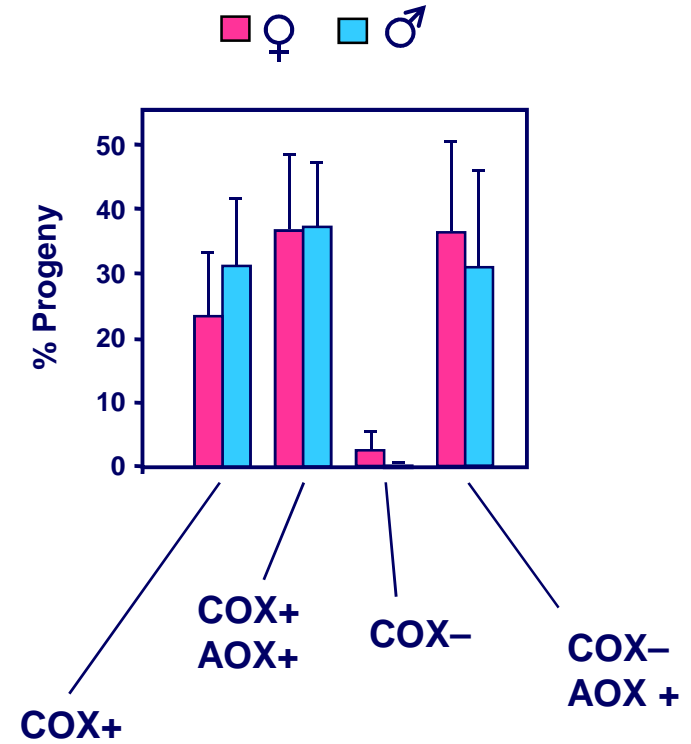
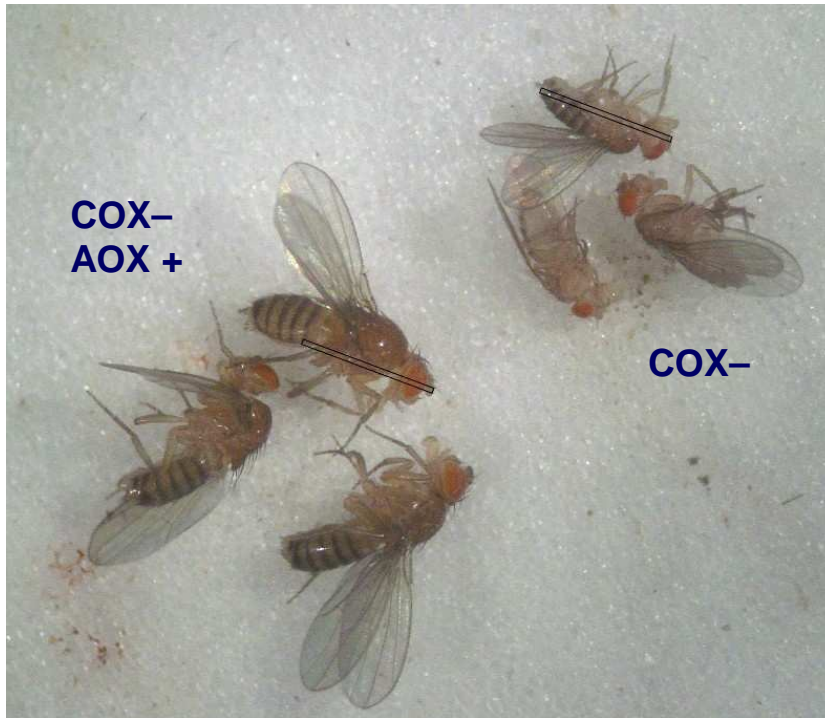


AOX renders flies resistant to cyanide and other mitochondrial poisons

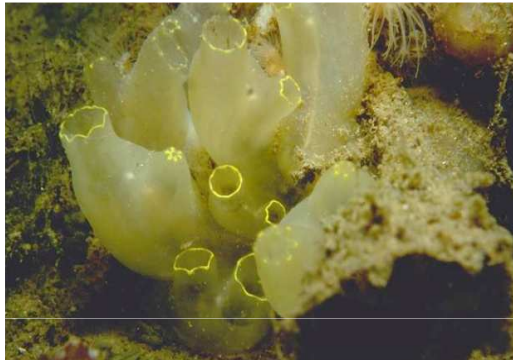


in 30 µg/ml antimycin

AOX cures the growth defect and high lethality of COX deficiency in flies



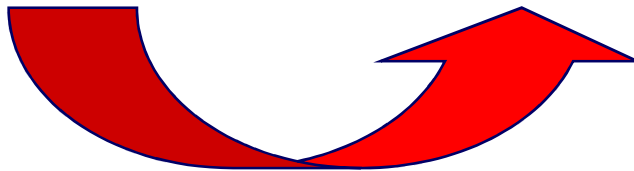
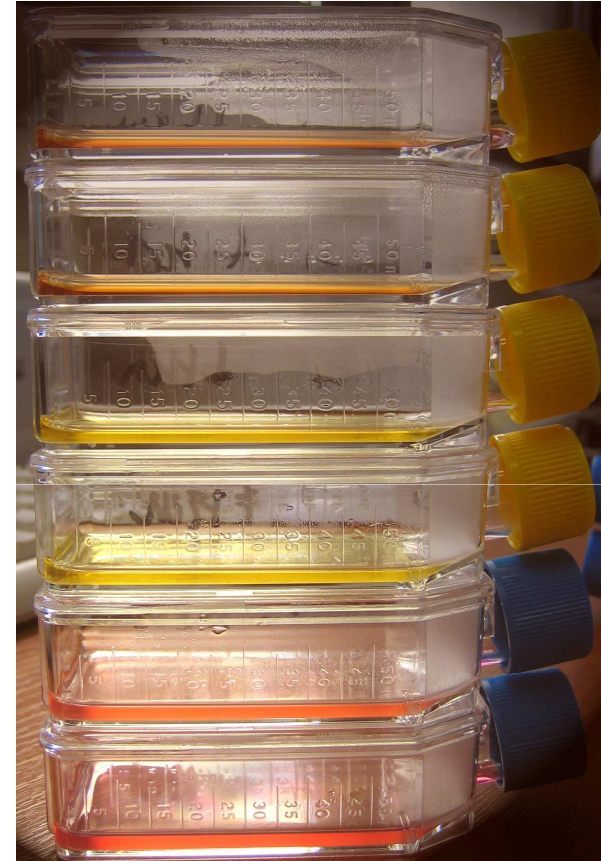
The Alternative Oxidase



from the sea squirt

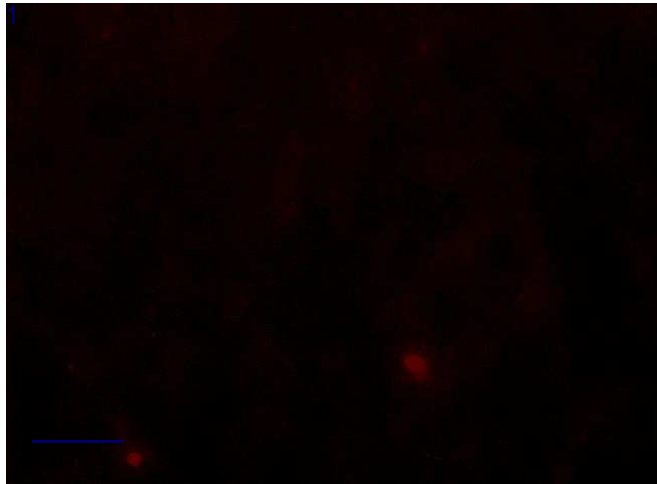
AOX

to cultured human cells

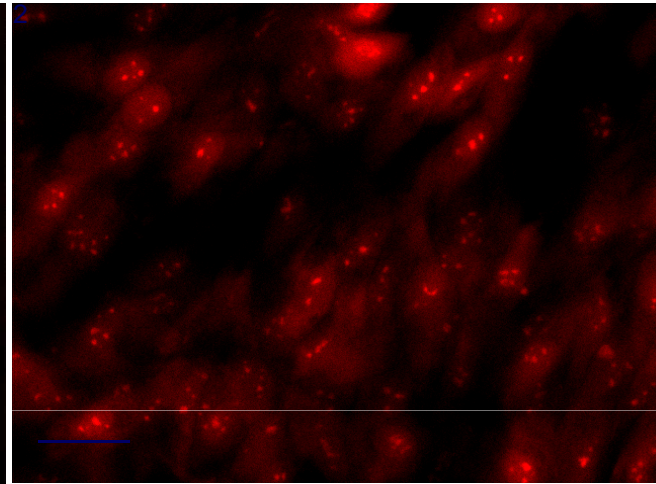


AOX alleviates oxidative stress caused by COX deficiency in patients' cells

healthy



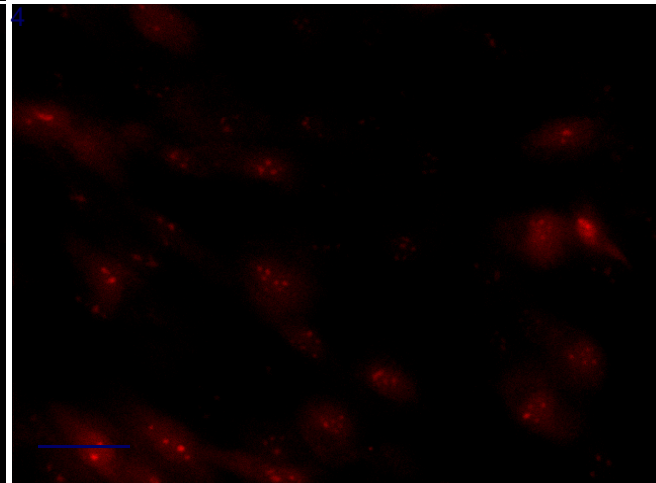
patient



healthy
+ AOX



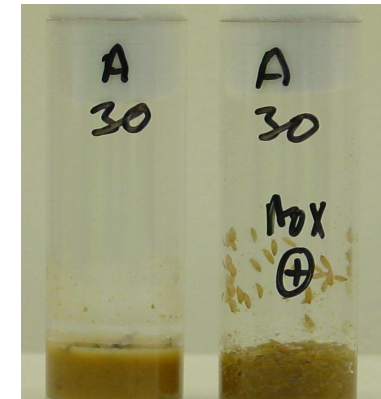
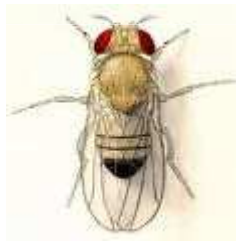
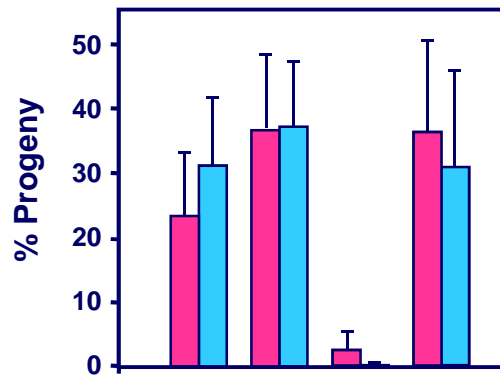
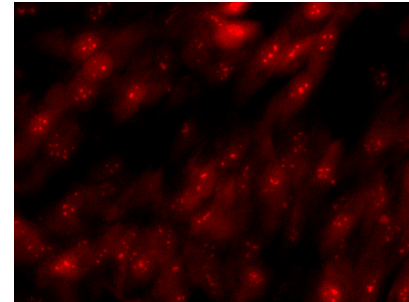
patient
+ AOX



AOX shows promise in flies and cells



AOX

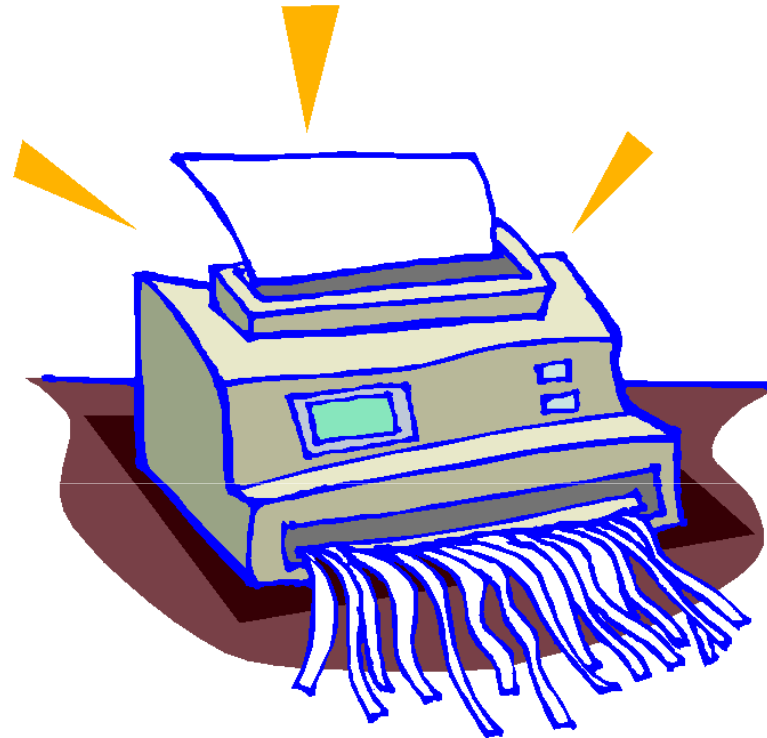


- Dassa E et al. (2009) *EMBO Molecular Medicine* (in press)
- Fernandez-Ayala DJM et al. (2009) *Cell Metabolism* (in press)
- Rustin P & Jacobs HT (2009) *Physiologia Plantarum* (in press)

My experience of the ERC process

as applicant

- light applications procedure
- focus on science
- easy online system
- good feedback
- emphasis on novelty and riskiness
- success !



My experience of the ERC process

as grantholder



- serious money (what I requested)
- relatively simple 'contract negotiation'
- odd and cumbersome reporting schedule
- science seems to be what counts
- too early to say much more

My experience of the ERC process

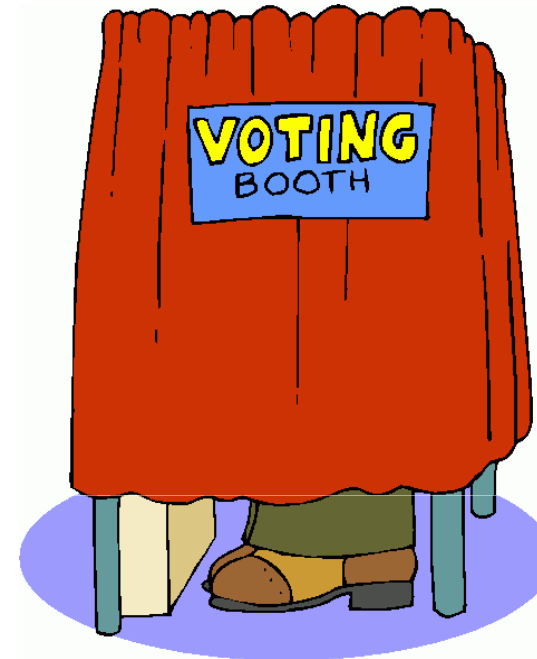
as panellist / reviewer

- high standard of applicants
- eligibility criteria a bit haphazard
- not attracting enough good females
- few credible applications outside of major countries
- transparent review procedure
- scientific quality and originality are what count



My experience of the ERC process

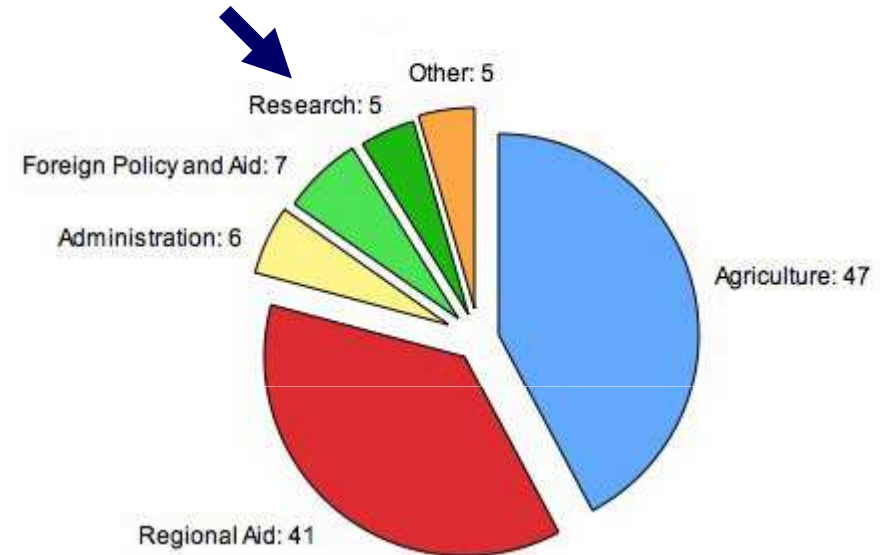
as citizen



- value for money
- rewards and nurtures excellence
- much less bureaucracy (though still not perfect)
- promotes infrastructure investment
- independent of lobbying, government policy or spurious ideology

What can individual countries do to increase their scientists' chances ?

lobby for programme expansion



- more budget for research and less for farmers
- strengthen ERC and abolish everything else
- resist any return to *juste retour*

What can individual countries do to increase their scientists' chances ?

promote mobility and careers of young stars



- generous grants for outward mobility of PhD students and postdocs
- based on academic credentials of scholar and host lab / institution
- generous grants for successful returnees + tenure track opportunities
- gender equality in deed as well as word

What can individual countries do to increase their scientists' chances ?

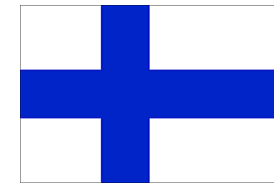
**strengthen national
research infrastructure**



- **good infrastructure will attract and motivate good scientists**
- **quality of the research environment is one of the evaluated criteria**
- **in the long run, ERC grants will go to the countries that invest the most**

What can individual countries do to increase their scientists' chances ?

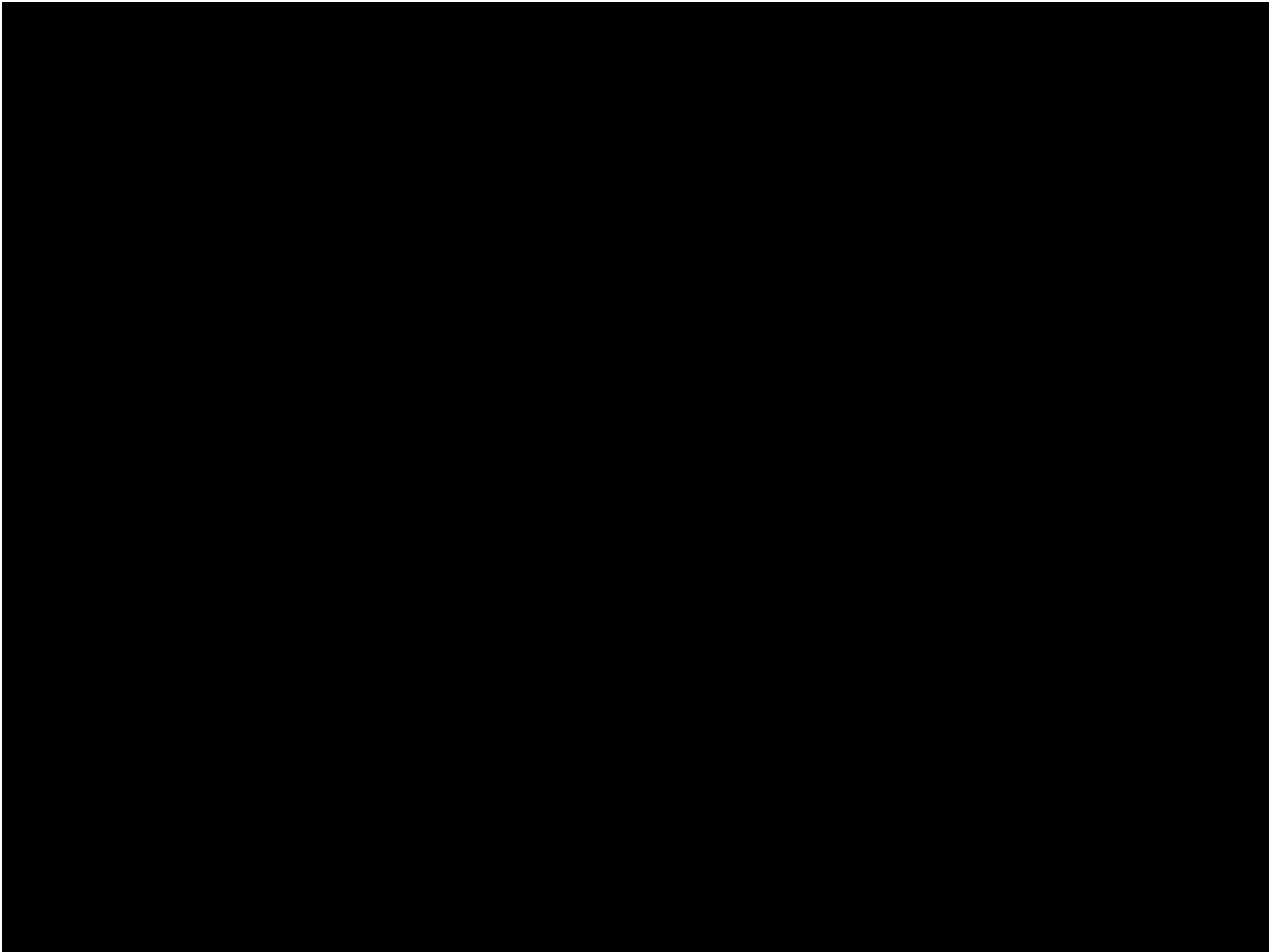
adopt ERC principles for national science funding



- excellence (track record and research plans) but not seniority
- stress on originality and novelty
- non-prescriptive funding
- transparent international peer-review
- substantial and long-term (5-year) financing
- measure success and reward the successful institutions
- follow the lead of countries that already implement such policies

Thank-you !





EMBO reports



- short-format papers on ground-breaking discoveries in molecular life sciences
 - main findings must be self-contained and of wide general interest
 - plus scientific commentaries, reviews and 'science-and society' articles
 - a more focussed competitor for *Nature*
 - fast turn-around for all manuscripts
-
- *EMBO reports* aims at a similar profile as the life sciences projects supported by ERC: novelty, impact, cross-disciplinarity, excellence