

Perspectives in antimicrobial agents

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Slides are available on <http://www.facm.ucl.ac.be> → Lectures

What its all about ?

- Is there a crisis in antibiotic research and development ?
- What has been introduced recently ?
- What is in the pipeline ?
- What are the hurdles ?
- Towards a really new approach ?

The antibiotic crisis *

1. Resistance

- * A pictorial view using 4 paintings of Van Gogh (who stayed briefly in Belgium when moving from Holland to France) and with selected Belgian and International data...

Are antibiotics following a path to madness ?



discovery in soil bacteria and fungi

1928 - ...

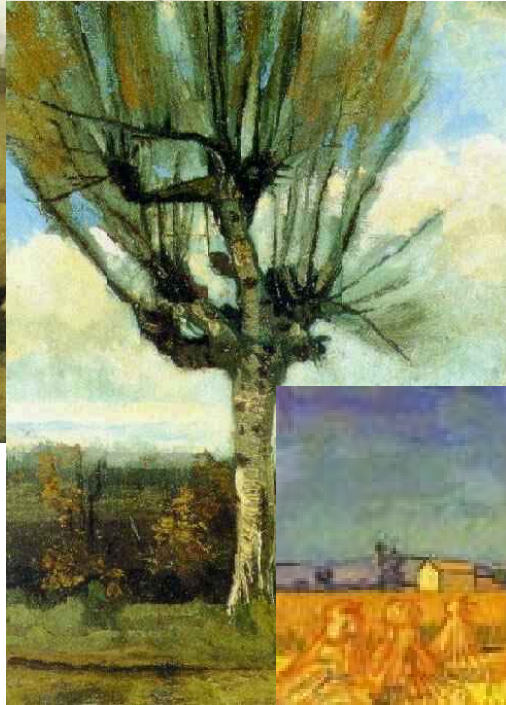
Are antibiotics following a path to madness ?



and then we all saw the
blooming tree of semi-
synthetic and totally synthetic
antibiotics

1950 – 1980 ...

Are antibiotics following a path to madness ?



**and the US General Surgeon
told us that the fight was over**

1970 ...

Are antibiotics following a path to madness ?

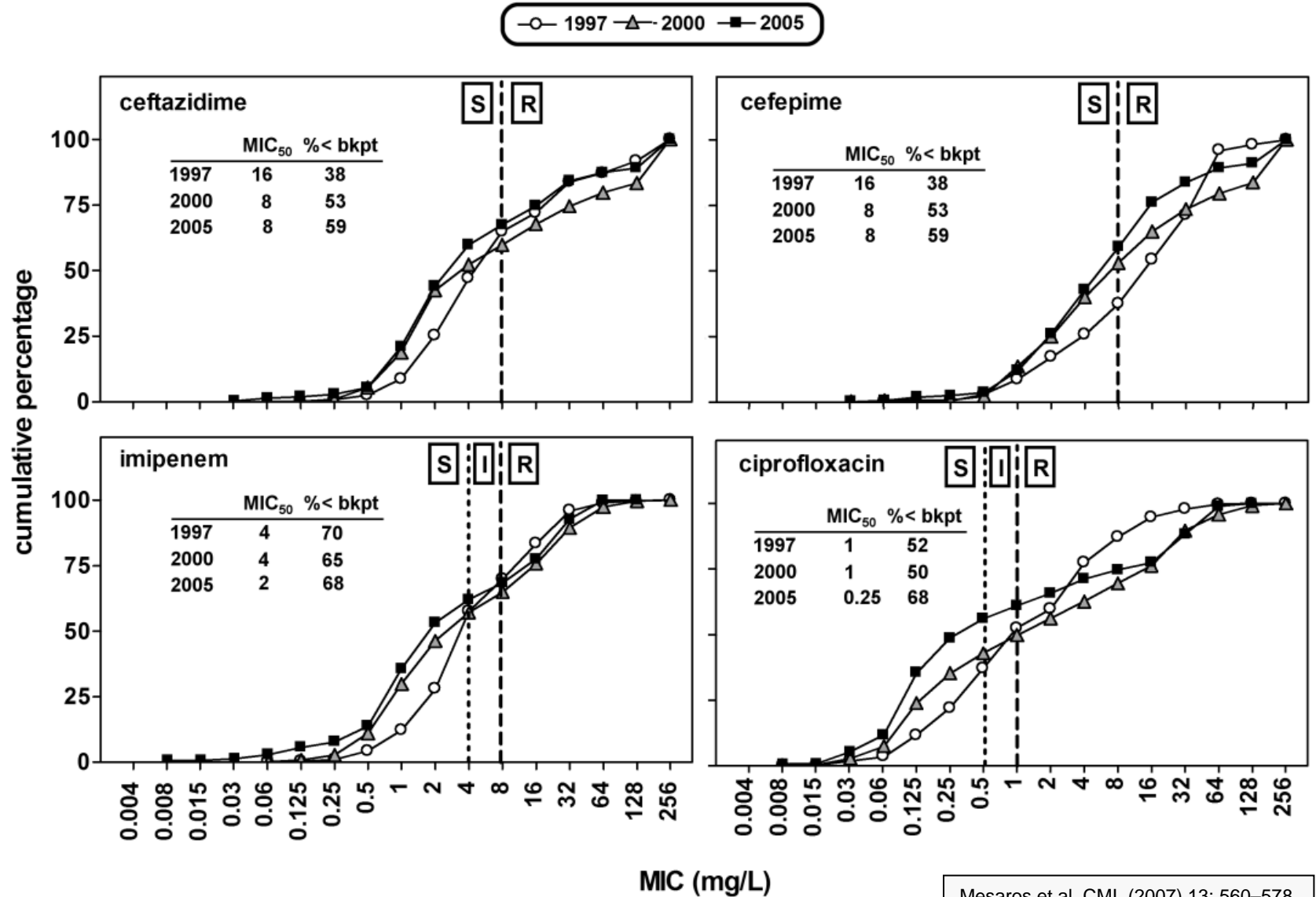


But...

2012 ...

Extent of resistance of *P. aeruginosa*

(International data – EUCAST breakpoints)



Mesaros et al. CMI, (2007) 13: 560–578

The hidden risk of therapy (at the corner of your street ...)

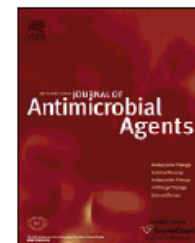
International Journal of Antimicrobial Agents 36 (2010) 513–522



Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: <http://www.elsevier.com/locate/ijantimicag>



In vivo development of antimicrobial resistance in *Pseudomonas aeruginosa* strains isolated from the lower respiratory tract of Intensive Care Unit patients with nosocomial pneumonia and receiving antipseudomonal therapy

Mickaël Riou^{a,1}, Sylviane Carbonnelle^{a,2}, Laëtitia Avrain^{a,b}, Narcisa Mesaros^{a,3}, Jean-Paul Pirnay^c, Florence Bilocq^c, Daniel De Vos^{c,d}, Anne Simon^e, Denis Piérard^f, Frédérique Jacobs^g, Anne Dediste^h, Paul M. Tulkens^{a,*}, Françoise Van Bambeke^a, Youri Glupczynskiⁱ

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^c Laboratory for Molecular & Cellular Technology, Queen Astrid Military Hospital, Neder-over-Heembeek, Brussels, Belgium

^d Department of Molecular and Cellular Interactions, Vrije Universiteit Brussel, Brussels, Belgium

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^g Clinique des Maladies Infectieuses, Hôpital Erasme, Brussels, Belgium

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ⁱ Laboratoire de Microbiologie, Cliniques Universitaires UCL de Mont-Godinne, Yvoir, Belgium

Question #1: are you effective ?

Assessment of adequateness of initial therapy

	No. of patients	No. of adequate antibiotics/total	% (no.) of patients with adequate therapy (EUCAST)
Monotherapy	26	1/1	57.7 (15)
2 antibiotics	14	2/2	71.4 (10)
3 antibiotics	13	3/3	38.5 (5)
4 antibiotics	1	3/4	100(1)

Message #1: many patients receive ineffective antibiotics

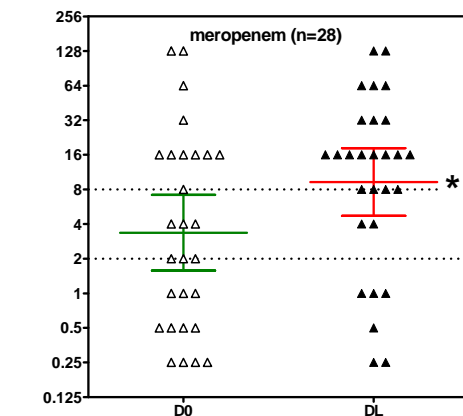
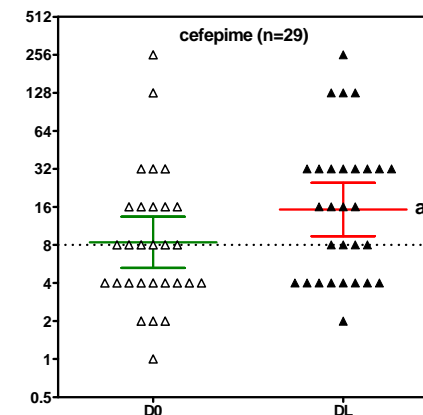
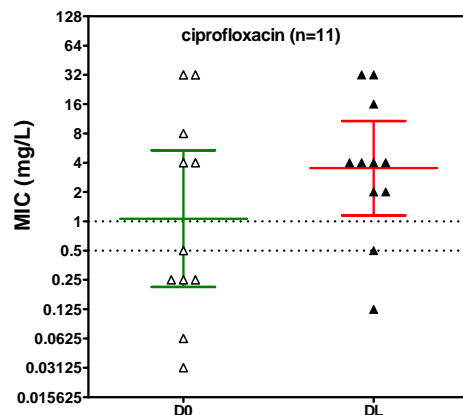
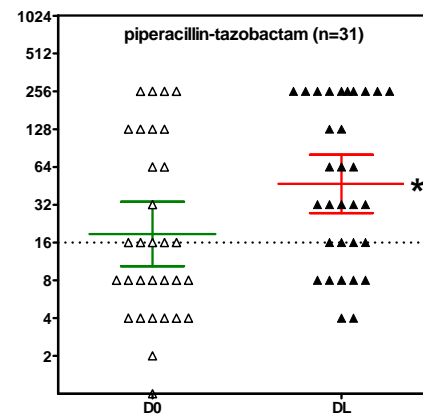
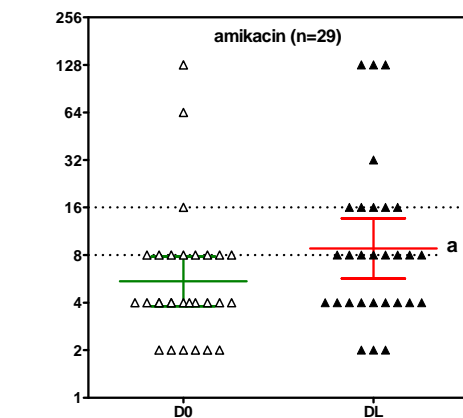
Question #2: do you remain effective while treating ?

- D0: initial isolate
DL: last isolate obtained
- individual values with geometric mean (95 % CI)
- S (lowest line) and R (highest line) EUCAST breakpoints

* $p < 0.05$ by paired t-test (two-tailed) and Wilcoxon non-parametric test

^a $p < 0.05$ by Wilcoxon non-parametric test only

Note: stratification by time between D0 and DL gave no clue (too low numbers)

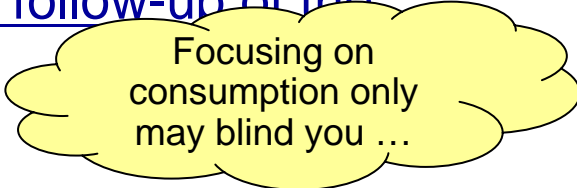


Message #2: for all antibiotics, we see global increases of MIC during treatment

Is there a crisis in antibiotic research?

Resistance **IS** a problem ...

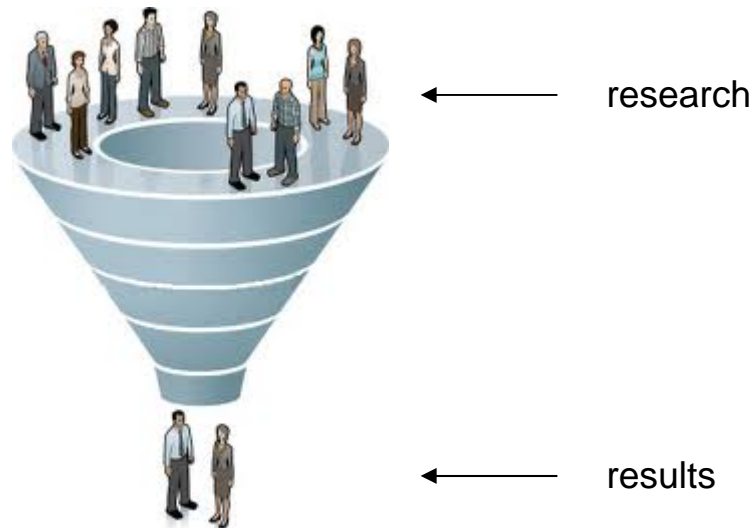
- The choices of effective therapies is narrowing dangerously for several important pathogens
- The Clinical pharmacist will have a key role in
 - Rationalizing the choice among the remaining ones
 - Optimizing those "remaining antibiotics"
 - Decreasing the inappropriate use of antibiotics whenever possible and improving hygiene with close follow-up of the epidemiology



Focusing on
consumption only
may blind you ...

Is there a crisis in antibiotic research ?

The drying pipeline ?



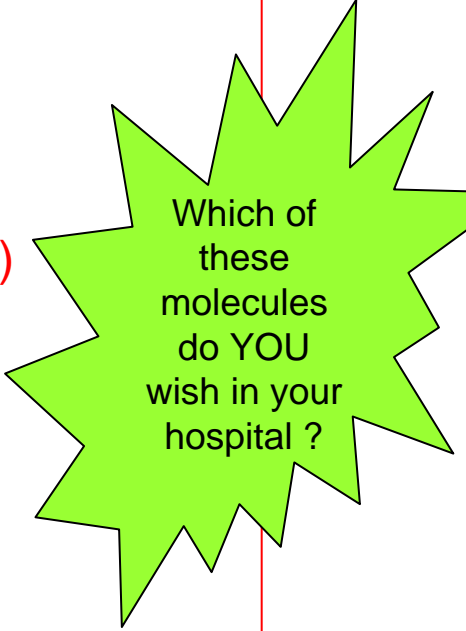
Is there a crisis in antibiotic research ?

2. the drying pipeline (1)

- Everyone speaks about the reduction in the number of new antibiotics... What is your reality ?

New antibiotics introduced in the Belgian market since 2000 in ATC code J01

- J01A tetracyclines..... 1 (tigecycline [Pfizer])
- J01B phenicols 0
- J01C β -lactams (penicillins)..... 0
- J01D other β -lactams 1 (doripenem [Janssen-Cilag])
- J01E sulfamides/trimethoprim:... 0
- J01F macrolides/linc./streptogr.: 1 (telithromycin [Sanofi])
- J01G aminoglycosides..... 0
- J01M quinolones..... 1 (moxifloxacin [Bayer])
- J01R associations:..... 0
- J01X others:..... 1 (linezolid [Pfizer])



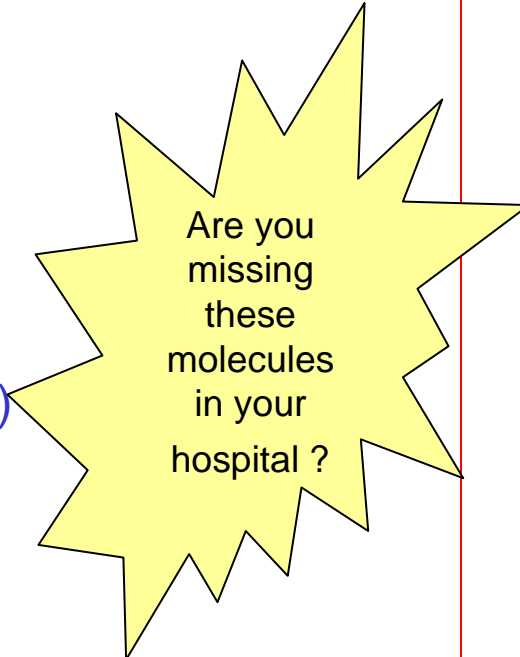
Which of these molecules do YOU wish in your hospital ?

Is there a crisis in antibiotic research ?

2. the drying pipeline (2)

New antibiotics in ATC code J01 and with EMA approval but **not available** in Belgium

- J01A tetracyclines.....0
- J01B phenicols0
- J01C β -lactams (penicillins).....0 (sulbactam [Pfizer])
- J01D other β -lactams1 (ertapenem [MSD])
- J01E sulfamides/trimethoprim:... 0
- J01F macrolides/linc./streptogr.: 1 (quinupristin/dalfopristin)
- J01G aminoglycosides.....0
- J01M quinolones.....0
- J01R associations:.....0
- J01X others:.....2 (daptomycin [Novartis])
(telavancin [Astellas])



Are you
missing
these
molecules
in your
hospital ?

* in at least one EU country since 2000 and with at least some advantages/differences with comparators

Colistin synergy: a surprising observation with sulbactam ...





International Journal of Antimicrobial Agents

Volume 39, Issue 2, February 2012, Pages 180–181



Letter to the Editor

Synergistic activity of sulbactam combined with colistin against colistin-resistant *Acinetobacter baumannii*

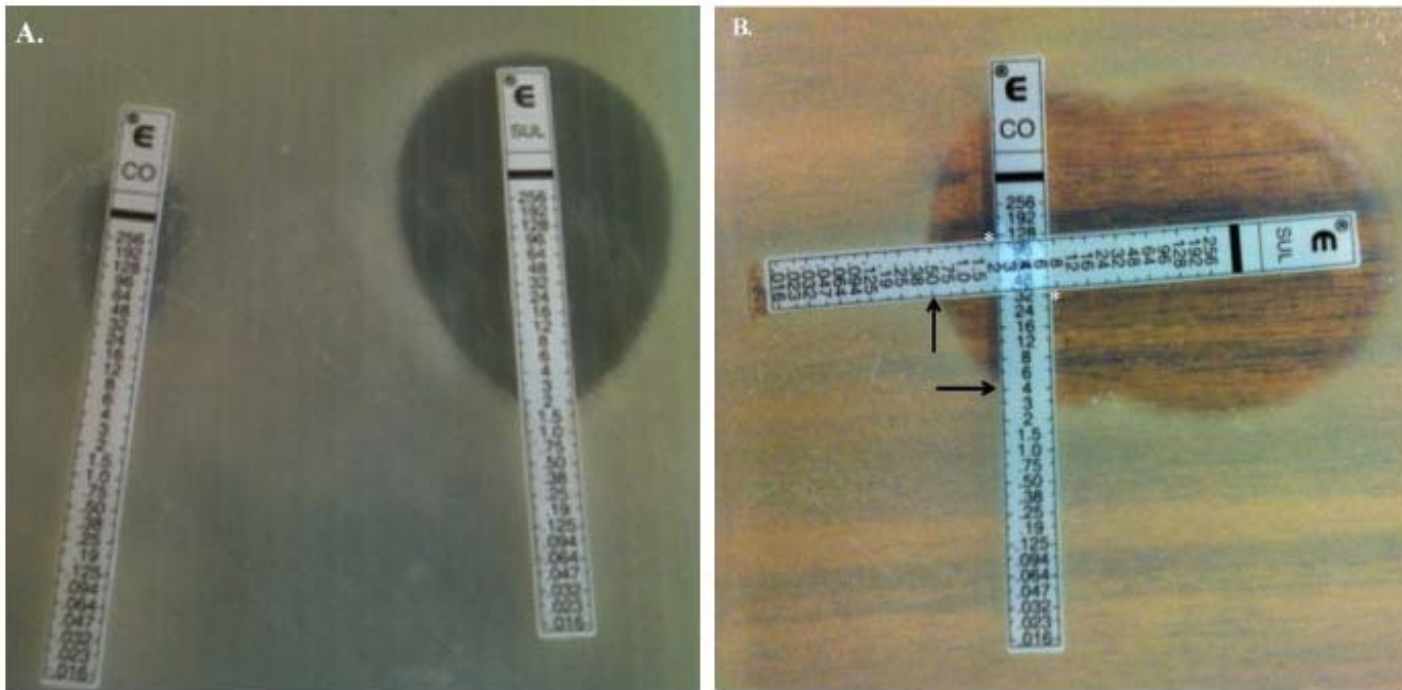
Marie Kempf, Lamia Djouhri-Bouktab, Jean-Michel Brunel, Didier Raoult, Jean-Marc Rolain  

Aix-Marseille Université, URMITE CNRS-IRD, UMR 6236, Faculté de Médecine et de Pharmacie, Université de la Méditerranée

Aix-Marseille-II, 27 Bd Jean Moulin, 13385 Marseille cedex 05, France

Received 29 September 2011. Available online 17 November 2011.

Colistin synergy with sulbactam




Colistin and sulbactam minimal inhibitory concentrations (MICs) of the colistin-resistant *Acinetobacter baumannii* strain as determined by Etest: colistin, 32 mg/L; sulbactam, 2 mg/L. (B) Synergy as shown by Etest; the colistin MIC is decreased from 32 mg/L to 4 mg/L and the sulbactam MIC is decreased from 2 mg/L to 0.5 mg/L, as indicated by arrows (asterisks denote original MICs).

Is there a crisis in antibiotic research ?

2. the drying pipeline (3)

New antibiotics in ATC code J01 and in the pipeline/waiting for EMA approval *

- J01A tetracyclines..... 1 → amadacycline (PTK 0796)
- J01B phenicols 0
- J01C β -lactams (penicillins)..... 0
- J01D other β -lactams 3 → ceftobiprole, ceftaroline
- J01E sulfamides/trimethoprim:... 0 → iclaprim
- J01F macrolides/linc./streptogr.: 1 → solithromycin, cethromycin
- J01G aminoglycosides..... 0 → plazomycin (ACHN-490)
- J01M quinolones..... 0 → several...
- J01R associations:..... 0 → avibactam (+ cephalosporins)
- J01X others:..... 2 → oritavancin, dalbavancin



Ever heard
about those
ones ?

* not an exhaustive list

Is there a crisis in antibiotic research ?

2. the drying pipeline (4)

New molecules in preclinical/early clinical development *

- New oxazolidinones (tedizolid, radezolid ...) active against LZDR strains
- New aminoglycosides active against AMGR strains (including arm) (**)
- New fluroquinolones active against MRSA (including CIPR strains)
- New gyrase inhibitors active against CIPR Gram(-) bacteria (**)
- New pleuromutilins (active against Gram + bacterial)
- New anti-MRSA carbapenems
- New lipopeptides (not affected by lung surfactant)
- New polymyxins derivatives (potentially less toxic)
- New ligase inhibitors (new target)

• ...



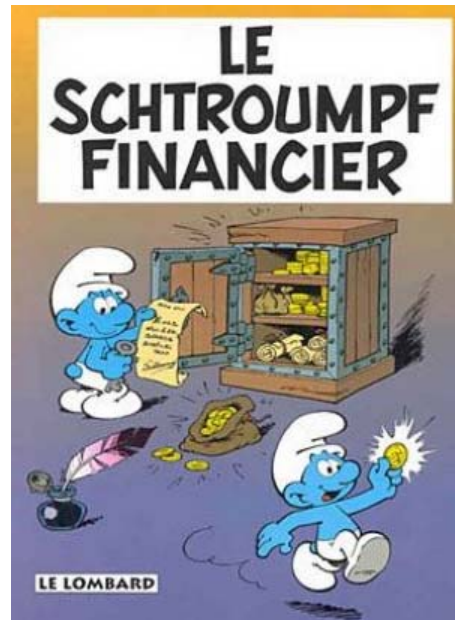
* not an exhaustive list

** DOD/NIH program

Is the pipeline really dry ?

- Not really, but...
 - Discovery **IS** difficult...
 - Preclinical development **IS** challenging...
 - but the real bottleneck is **clinical development** and **registration**...

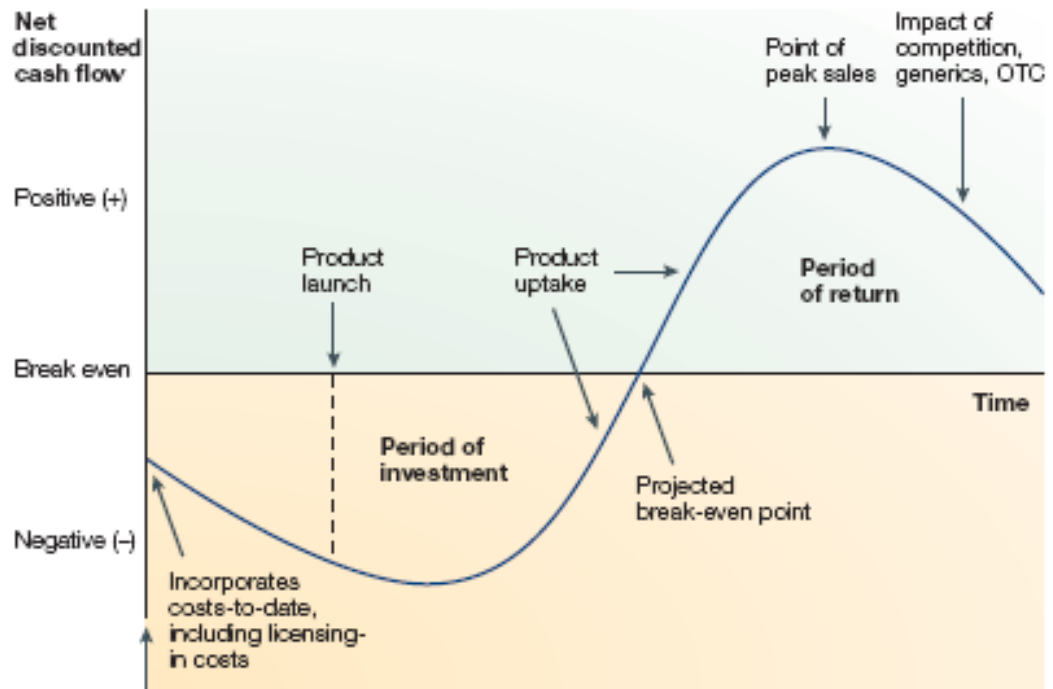
This is a main part
of the problem
(in our current
situation)



Why is economy important ?

- Can you work without support ? ...
 - You need investors
 - Those will ask some return at some point...
 - And none ignores what is a ROI

This is what every economist will tell you (and you know it !)



So, what are the hurdles ?

- Discovery !
 - More efforts must be made with both public and private funding
- Clinical development
 - We must strive to efforts that are really meaningful (but this may command a smaller market ... see hereunder)
- Registration
 - Provisional registration must be warranted for really innovative compounds (at phase II level) if helping to solve unmet medical needs
 - Safety issues must remain of paramount importance but should not deter honest efforts (no drug is harmless !)

So, what are the hurdles ?

- Discovery !
 - More efforts must be made with both public and private funding

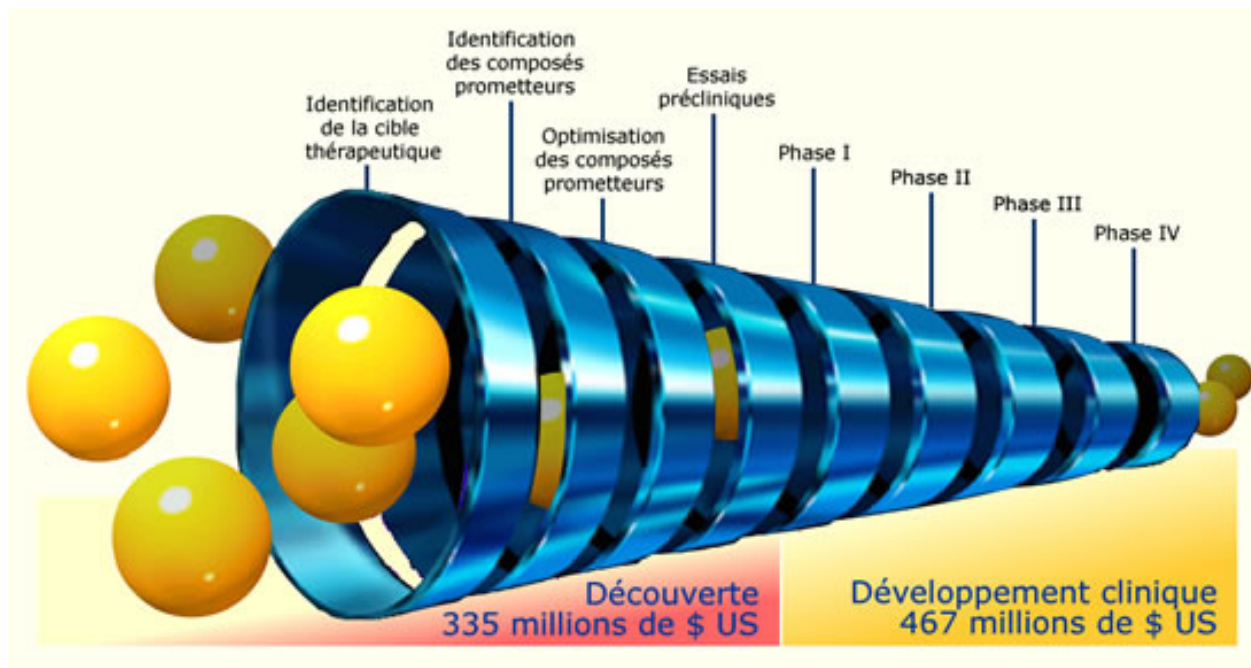


Today, several new antibiotic programs are financed by the US DOD ...

But NIH (and EU...) programs are catching up...

So, what are the hurdles ?

- Clinical development
 - We must strive to efforts that are really meaningful (but this may command a smaller market ... see hereunder)

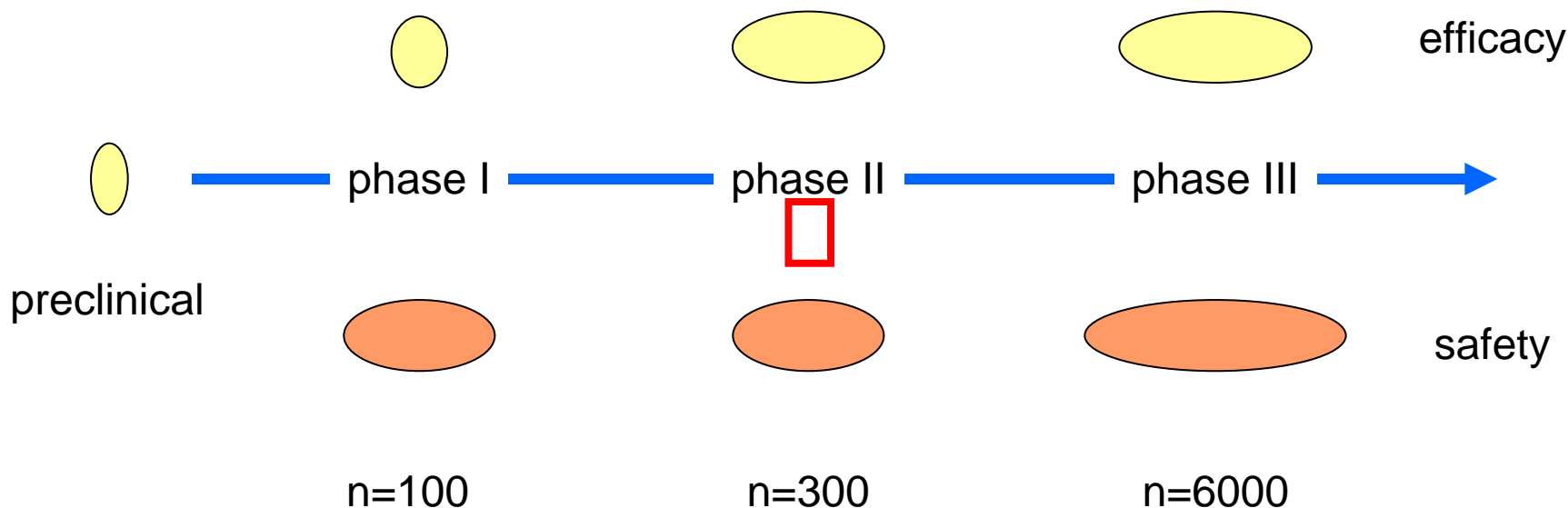


Let us stop this !
(but its not the Industry's fault only !)

So, what are the hurdles ?

- Registration

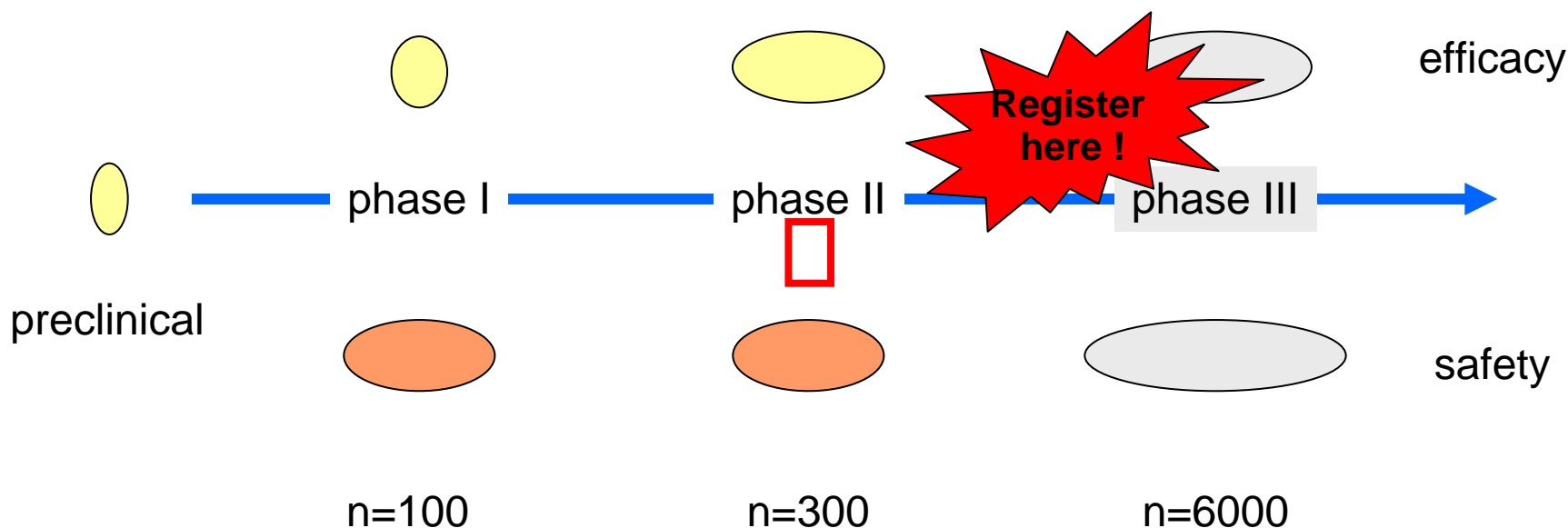
- Provisional registration must be warranted for really innovative compounds (at phase II level) if helping to solve unmet medical needs (and be accepted for that !)
- Safety issues must remain of paramount importance but should not deter honest efforts (no drug is harmless !)



So, what are the hurdles ?

- Registration

- Provisional registration must be warranted for really innovative compounds (at phase II level) if helping to solve unmet medical needs (and be accepted for that !)
- Safety issues must remain of paramount importance but should not deter honest efforts (no drug is harmless !)



One new drug (tedizolid)...

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2011, p. 583–592
0066-4804/11/\$12.00 doi:10.1128/AAC.00076-10
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Vol. 55, No. 2

Phase 2, Randomized, Double-Blind, Dose-Ranging Study Evaluating the Safety, Tolerability, Population Pharmacokinetics, and Efficacy of Oral Torezolid Phosphate in Patients with Complicated Skin and Skin Structure Infections^{▽†‡}

P. Prokocimer,^{1*} P. Bien,¹ J. Surber,² P. Mehra,³ C. DeAnda,¹ J. B. Bulitta,⁴ and G. R. Corey⁵

Trius Therapeutics, Inc., 6310 Nancy Ridge Road, Suite 105, San Diego, California 92121¹; SERRG, Inc., 5210 Armour Road Suite 400, Columbus, Georgia 31904²; eStudy Site, 752 Medical Center Court, Suite 105, Chula Vista, California 91911³; Ordway Research Institute, 150 New Scotland Avenue, Albany, New York 12208⁴; and Duke Clinical Research Institute, 2400 Pratt Street, Durham, North Carolina 27705⁵

Received 19 January 2010/Returned for modification 9 June 2010/Accepted 2 November 2010

Torezolid (TR-700) is the active moiety of the prodrug torezolid phosphate ([TP] TR-701), a second-generation oxazolidinone with 4- to 16-fold greater potency than linezolid against Gram-positive species including methicillin-resistant *Staphylococcus aureus* (MRSA). A double-blind phase 2 study evaluated three levels (200, 300, or 400 mg) of oral, once-daily TP over 5 to 7 days for complicated skin and skin structure infections (cSSSI). Patients 18 to 75 years old with cSSSI caused by suspected or confirmed Gram-positive pathogens were randomized 1:1:1. Of 188 treated patients, 76.6% had abscesses, 17.6% had extensive cellulitis, and 5.9% had wound infections. *S. aureus*, the most common pathogen, was isolated in 90.3% of patients (139/154) with a baseline pathogen; 80.6% were MRSA. Cure rates in clinically evaluable patients were 98.2% at 200 mg, 94.4% at 300 mg, and 94.4% at 400 mg. Cure rates were consistent across diagnoses, regardless of lesion size or the presence of systemic signs of infection. Clinical cure rates in patients with *S. aureus* isolated at baseline were 96.6% overall and 96.8% for MRSA. TP was safe and well tolerated at all dose levels. No patients discontinued treatment due to an adverse event. Three-stage hierarchical population pharmacokinetic modeling yielded a geometric mean clearance of 8.28 liters/h (between-patient variability, 32.3%), a volume of the central compartment of 71.4 liters (24.0%), and a volume of the peripheral compartment of 27.9 liters (35.7%). Results of this study show a high degree of efficacy at all three dose levels without significant differences in the safety profile and support the continued evaluation of TP for the treatment of cSSSI in phase 3 trials.

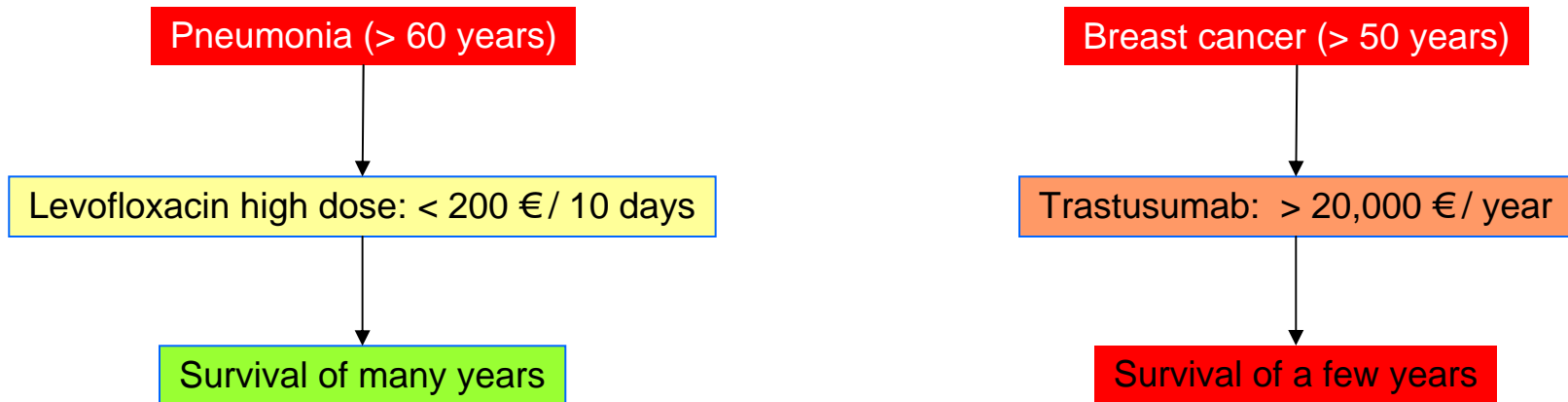
The weakness in this study is the lack of patients with LZD^R strains

So, what do you propose to do, now?

Other hurdles ?

- Pricing
 - Antibiotics are cheap...
 - And now, the Belgian pharmacist must deliver the cheapest one (generic)...
 - Why would Industry make an effort ?

Allow me to take a simple example...



Even better and it happened almost yesterday ...

Bij ontstentenis van een gemotiveerd definitief voorstel van de Commissie Tegemoetkoming Geneesmiddelen, binnen een termijn van 150 dagen wat betreft de specialiteit YERVOY 5 mg/ml, heeft de Minister, met toepassing van artikel 81 van het koninklijk besluit van 21 december 2001, een gemotiveerde beslissing genomen en genotificeerd op 22 maart 2012;

Ipilimumab

BELGISCH STAATSBLOED
MAANDAG 21 MEI 2012
Tweede editie

Benaming / Dénomination (Aanvrager / Demandeur)								
Cat.	Code	Verpakkingen	Conditionnements	Opm Obs	Prijs Prix <i>buiten bedrijf / ex- usine</i>	Basis v tegemoe Base de remb. <i>buiten bedrijf / ex-usine</i>	I	II
YERVOY 5 mg/ml		BRISTOL-MYERS SQUIBB BELGIUM			ATC: L01XC11			
	0751-081	1 injectieflacon 10 ml concentraat voor oplossing voor infusie, 5 mg/ml	1 flacon injectable 10 ml solution à diluer pour perfusion, 5 mg/ml		4250,0000	4250,0000		
A-28 *	0751-081	1 injectieflacon 10 ml concentraat voor oplossing voor infusie, 5 mg/ml	1 flacon injectable 10 ml solution à diluer pour perfusion, 5 mg/ml	T	4512,1100	4512,1100		
A-28 **	0751-081	1 injectieflacon 10 ml concentraat voor oplossing voor infusie, 5 mg/ml	1 flacon injectable 10 ml solution à diluer pour perfusion, 5 mg/ml	T	4505,0000	4505,0000		

Cost of treatment of one patient/year: 77 000 €

Is this not saving lives ?

Lancet Oncol. 2010 Feb;11(2):155-64. Epub 2009 Dec 8.

Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study.

Wolchok JD, Neyns B, Linette G, Negrier S, Lutzky J, Thomas L, Waterfield W, Schadendorf D, Smylie M, Guthrie T Jr, Grob JJ, Chesney J, Chin K, Chen K, Hoos A, O'Day SJ, Lebbé C.

Ludwig Center for Cancer Immunotherapy, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA. wolchokj@mskcc.org

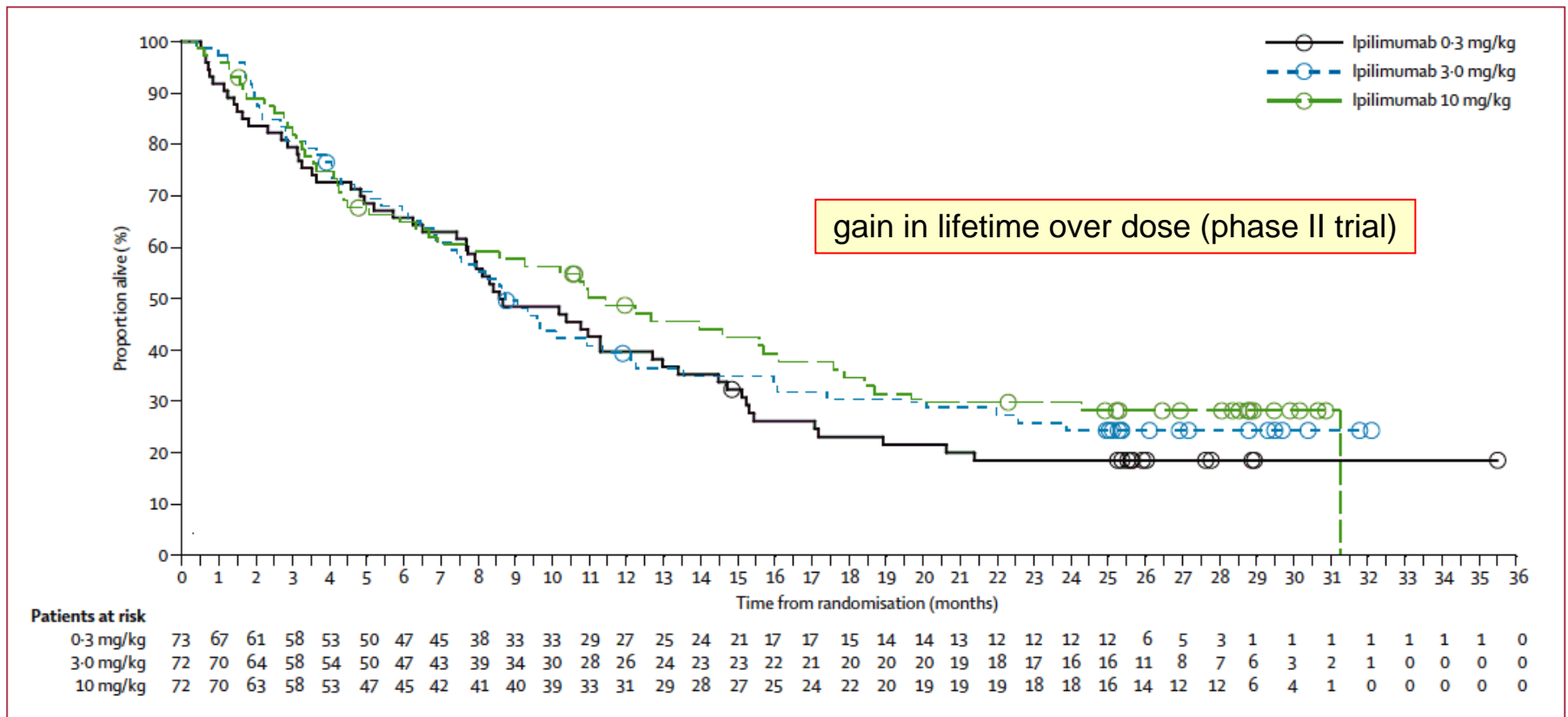
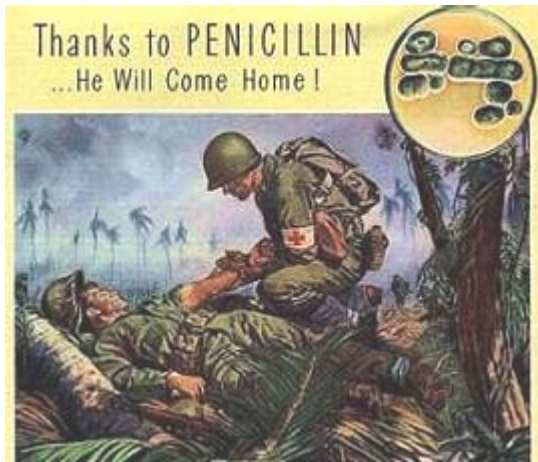


Figure 2: Kaplan-Meier estimate for overall survival, by treatment arm

Funding Bristol-Myers Squibb.

Do you remember having seen this ?



Penicillin saves lives

Pentrexyl (Bristol-Myers Squibb) ▲

[ampicilline (sodium)]
flacon i.m. - i.v. - perf.



1 x 2g poudre

R_x

b ○

€ 7,22

Are you
getting the
message ?

And Bristol-Myers will treat a patient (2 g/day; 10 days)
for 1 000 x cheaper than melanoma

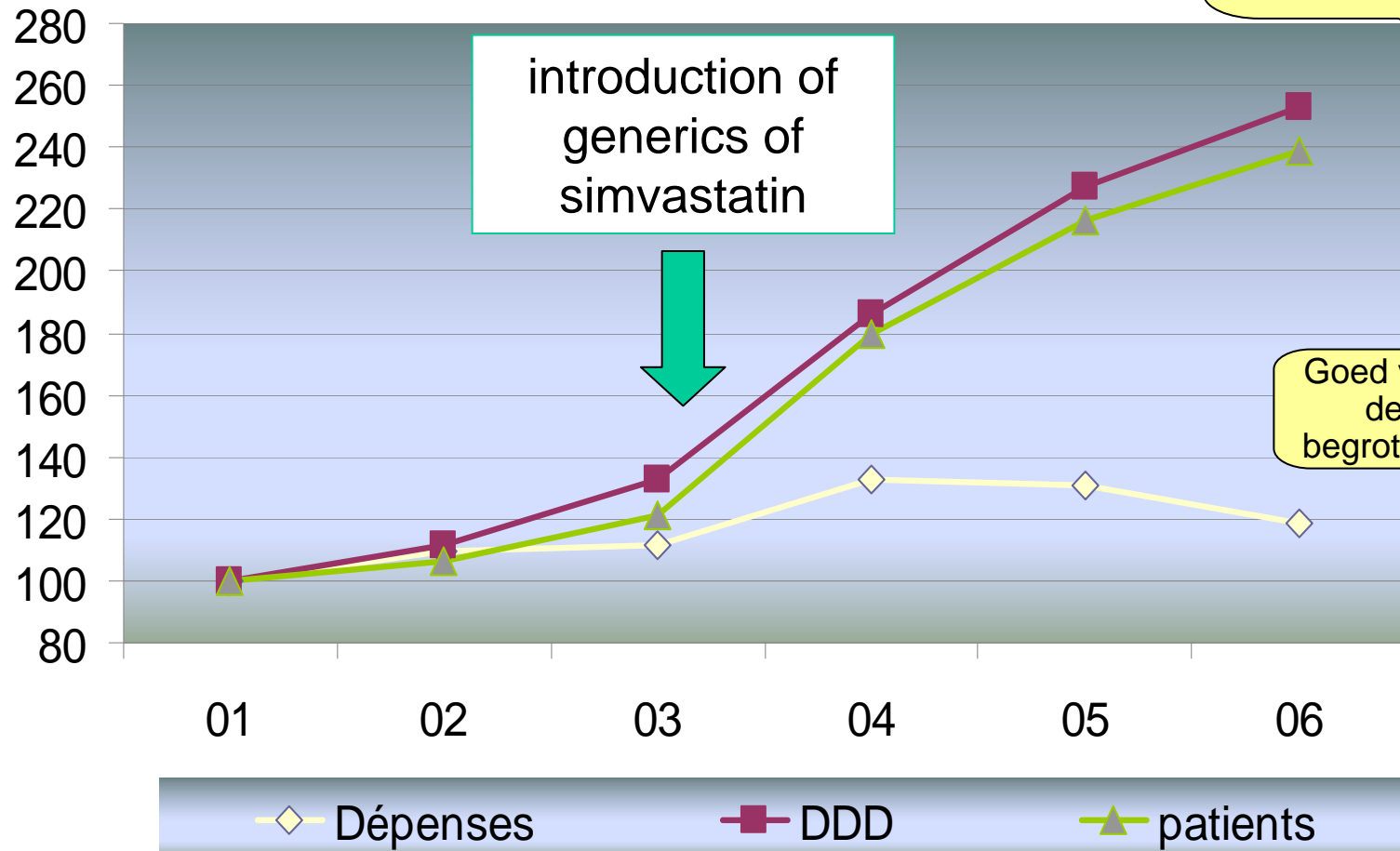
Is the cheapest the best ?



The increase in air travel associated with the development of cheap airlines is a important contributor to the rise in CO₂ levels and other pollutants in high atmosphere...

<http://www.cheapflights.co.uk/travel-tips/carbon-emissions/>

Increase in statins consumption over years in Belgium



Source: INAMI / RIZIV

Other approaches...

- **Old antibiotics...**

Old and discarded, or even rejected, antibiotics should be re-investigated, repurposed and used as needed. Pharmaceutical companies should provide their stocks for this purpose (retaining rights to other applications).

Bush et al. Tackling antibiotic resistance Nature Reviews Microbiology (2011) 9:894-896.

Journal of Antimicrobial Chemotherapy (2009) 63, 243–245

doi:10.1093/jac/dkn511

Advance Access publication 18 December 2008

JAC

Temocillin revived

David M. Livermore^{1*} and Paul M. Tulkens²

¹*Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK;* ²*Unité de Pharmacologie Cellulaire et Moléculaire & Centre de Pharmacie Clinique, Université Catholique de Louvain, Bruxelles, Belgium*

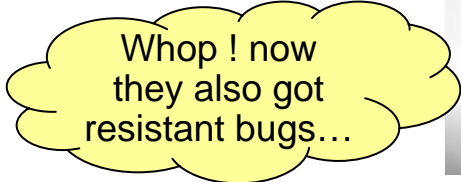
Resistance in Gram-negative pathogens is an increasing concern, with carbapenems often appearing as the only acceptable treatment option in serious infections. Reviving older compounds that have fallen into disuse may help to alleviate this burden. Temocillin (6- α -methoxy-ticarclillin) is resistant to most if not all classical and extended-spectrum β -lactamases and to AmpC enzymes. It is also chemically stable, allowing administration by continuous infusion. Pharmacokinetic/pharmacodynamic analysis, aided by Monte-Carlo simulations, suggests a breakpoint of 8 mg/L for the registered maximum dosage of 4 g daily. Temocillin's weaknesses, explaining its limited previous use, are a lack of activity against Gram-positive organisms, anaerobes and *Pseudomonas*. In settings where these are unlikely or are covered by other agents, temocillin may be useful, potentially 'sparing' carbapenems and having little apparent potential to select for *Clostridium difficile*.

How do you protect this drug ?

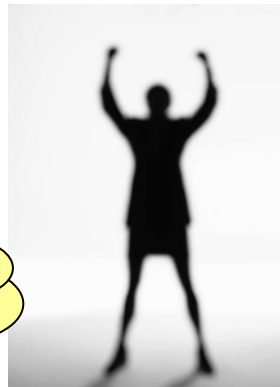


The problems with "old antibiotics": The case of colistin

- Is the dosage clearly defined ?
→ repeated dosage of 150 mg colistimethate (2×10^6 U or 66 mg colistin base) every 8h is probably the best option ... but more may be needed...
- Do we need a loading dose ?
→ additional 2 to 4 $\times 10^6$ U at first dose; total 4 to 6 $\times 10^6$ U and perhaps up to 8-9 but are we sure about that ???
- Do we have good breakpoints ? → No !
- Can we use in monotherapy ? → No !
- Do we need to test for susceptibility on a repeated fashion ... → Yes!
- Do we need to monitor the renal function and adjust the dosage:
→ Yes, but nobody really knows what to do exactly ...
- Remember that this is a last resource drug...
→ but the Greeks use a lot of it...



Whop ! now
they also got
resistant bugs...



The best study on colistin that the Industry did NOT make !

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3284–3294
0066-4804/11/\$12.00 doi:10.1128/AAC.01733-10
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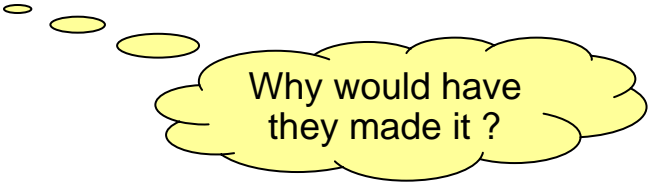
Vol. 55, No. 7

Population Pharmacokinetics of Colistin Methanesulfonate and Formed Colistin in Critically Ill Patients from a Multicenter Study Provide Dosing Suggestions for Various Categories of Patients[∇]

S. M. Garonzik,^{1†} J. Li,^{2†} V. Thamlikitkul,³ D. L. Paterson,⁴ S. Shoham,⁵ J. Jacob,² F. P. Silveira,^{6‡}
A. Forrest,^{1‡} and R. L. Nation^{2*‡}

School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, SUNY, Buffalo, New York¹; Facility for Anti-infective Drug Development and Innovation, Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, Australia²; Division of Infectious Diseases and Tropical Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand³; The University of Queensland Center for Clinical Research, Royal Brisbane and Women's Hospital, Brisbane, Australia⁴; Washington Hospital Center, MedStar Clinical Research Center, Washington, DC⁵; and Infectious Diseases, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania⁶

Received 13 December 2010/Returned for modification 13 March 2011/Accepted 28 April 2011



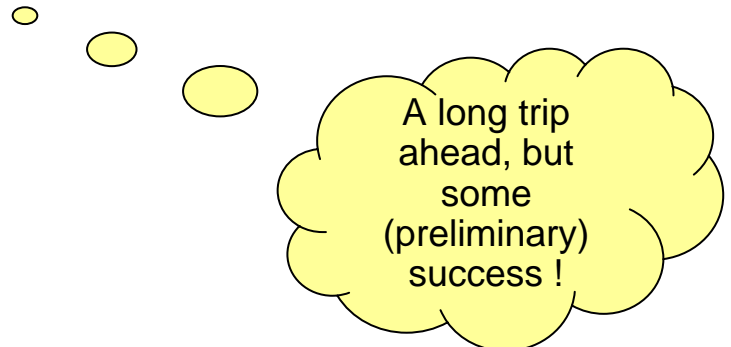
Why would have they made it ?

Other approaches...

- ***Alternatives to antibiotics.***

Novel non-antibiotic approaches for the prevention of and protection against infectious diseases should be encouraged, and such approaches must be high-priority research and development projects.

- antibacterial vaccines and immunotherapy,
- phage therapy,
- immunostimulants,
- adjuvants,
- antivirulence therapies,
- probiotics and their combinations



A long trip ahead, but some (preliminary) success !

Bush et al. Tackling antibiotic resistance Nature Reviews Microbiology (2011) 9:894-896.

Immunotherapy...

J Antimicrob Chemother 2011; **66**: 1110–1116

doi:10.1093/jac/dkr046 Advance Access publication 10 March 2011

Pharmacokinetics and safety of panobacumab: specific adjunctive immunotherapy in critical patients with nosocomial *Pseudomonas aeruginosa* O11 pneumonia

Qin Lu^{1†}, Jean-Jacques Rouby^{1†}, Pierre-François Laterre^{2*}, Philippe Eggimann³, Anthony Dugard⁴, Evangelos J. Giamarellos-Bourboulis⁵, Emanuelle Mercier⁶, Jorge Garbino⁷, Charles-Edouard Luyt⁸, Jean Chastre⁸, Violetta Georgescu-Kyburz⁹, Michael P. Rudolf⁹, Verena Gafner⁹, Hedvika Lazar⁹, Holger Koch⁹, Antonio Perez⁹, Stefanie D. Krämer¹⁰ and Michael Tamm¹¹

*Corresponding author. Professor Pierre-François Laterre, Intensive Care Unit, St Luc University Hospital, UCL, 10 Avenue Hippocrate, 1200 Brussels, Belgium. Tel: +32-2-764-2735; Fax: +32-2-764-2757; E-mail: laterre@rean.ucl.ac.be

†These authors contributed equally to this work.

Objectives: Nosocomial *Pseudomonas aeruginosa* pneumonia remains a major concern in critically ill patients. We explored the potential impact of microorganism-targeted adjunctive immunotherapy in such patients.

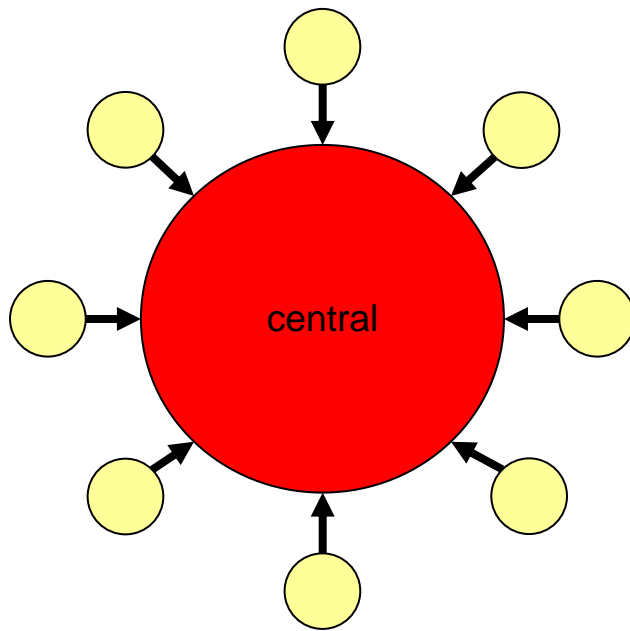
Patients and methods: This multicentre, open pilot Phase 2a clinical trial (NCT00851435) prospectively evaluated the safety, pharmacokinetics and potential efficacy of three doses of 1.2 mg/kg panobacumab, a fully human monoclonal anti-lipopolysaccharide IgM, given every 72 h in 18 patients developing nosocomial *P. aeruginosa* (serotype O11) pneumonia.

Results: Seventeen out of 18 patients were included in the pharmacokinetic analysis. In 13 patients receiving three doses, the maximal concentration after the third infusion was $33.9 \pm 8.0 \mu\text{g/mL}$, total area under the serum concentration–time curve was $5397 \pm 1993 \mu\text{g h/mL}$ and elimination half-life was $102.3 \pm 47.8 \text{ h}$. Panobacumab was well tolerated, induced no immunogenicity and was detected in respiratory samples. In contrast to Acute Physiology and Chronic Health Evaluation II (APACHE II) prediction, all 13 patients receiving three doses survived, with a mean clinical resolution in 9.0 ± 2.7 days. Two patients suffered a recurrence at days 17 and 20.

Conclusions: These data suggest that panobacumab is safe, with a pharmacokinetic profile similar to that in healthy volunteers. It was associated with high clinical cure and survival rates in patients developing nosocomial *P. aeruginosa* O11 pneumonia. We concluded that these promising results warrant further trials.

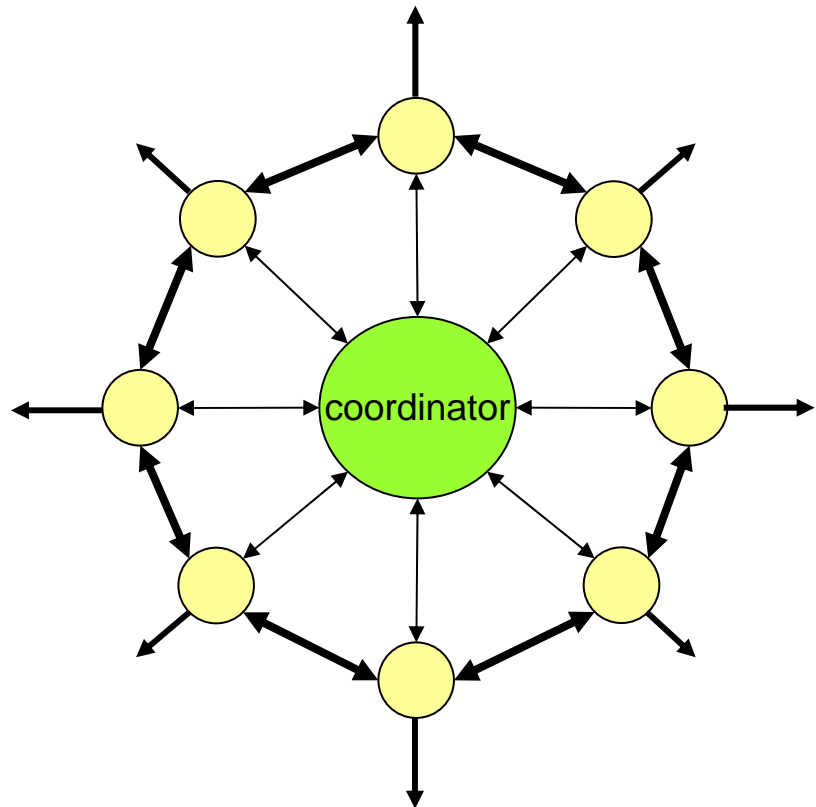
Are you going to invest in this drug ?

Towards a real scientific and economic (re)volution...



XBM network

Central science
Central economy



Internet

Network Science
Network economy

Enough of the *Université catholique de Louvain* ...

Lets us listen to the *Katholieke Universiteit Leuven*...

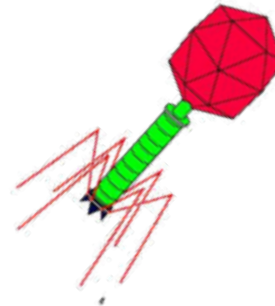
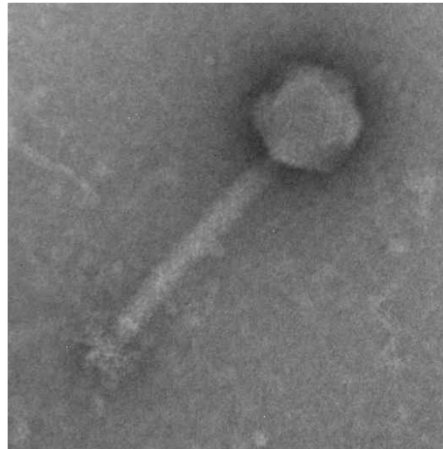
**Université
catholique
de Louvain**
<http://www.uclouvain.be>



**Katholieke
Universiteit
Leuven**
<http://www.kuleuven.be>

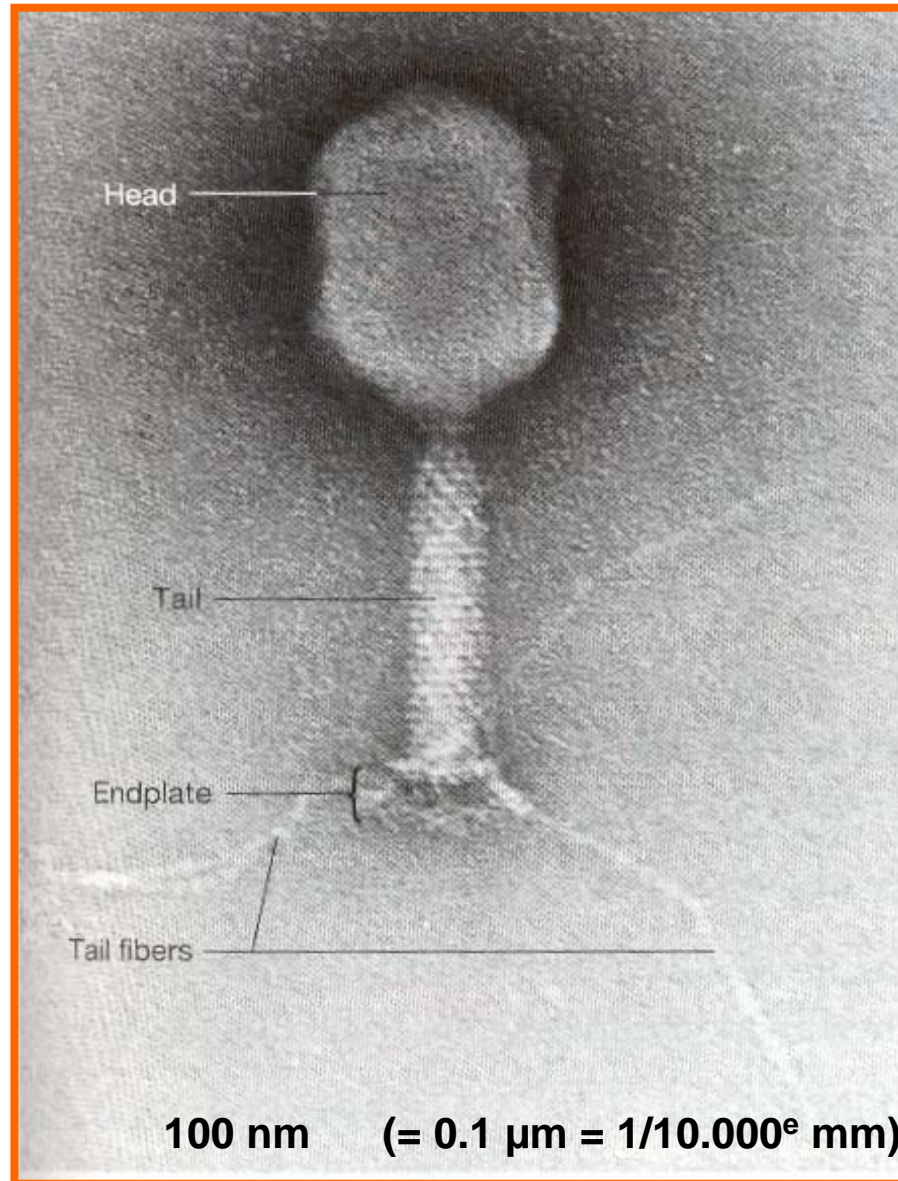
Bacteriophage therapy as an alternative?

- Bacteriophages

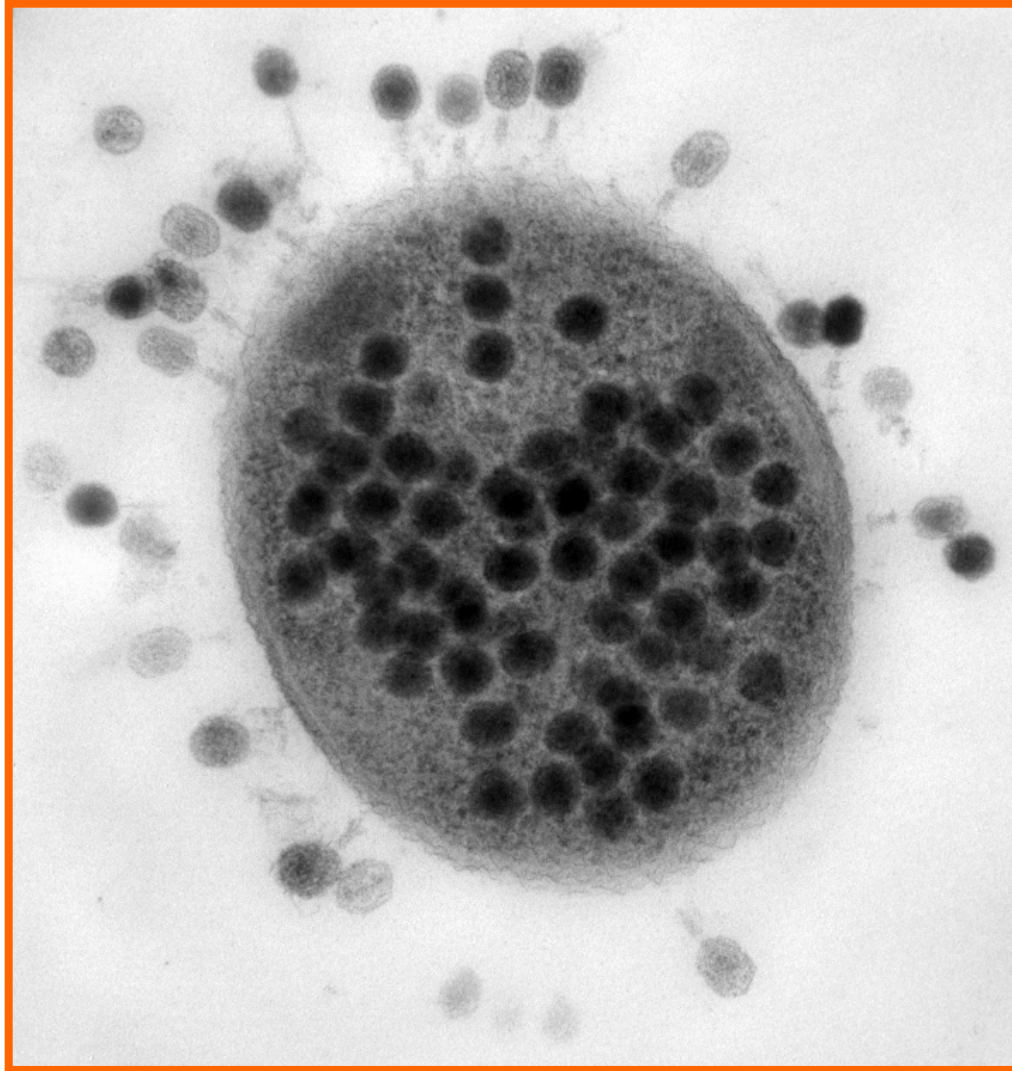


‘Viruses’ of bacteria (including “Superbugs”)
Co-evolving with bacteria
Natural enemies / controllers of bacteria

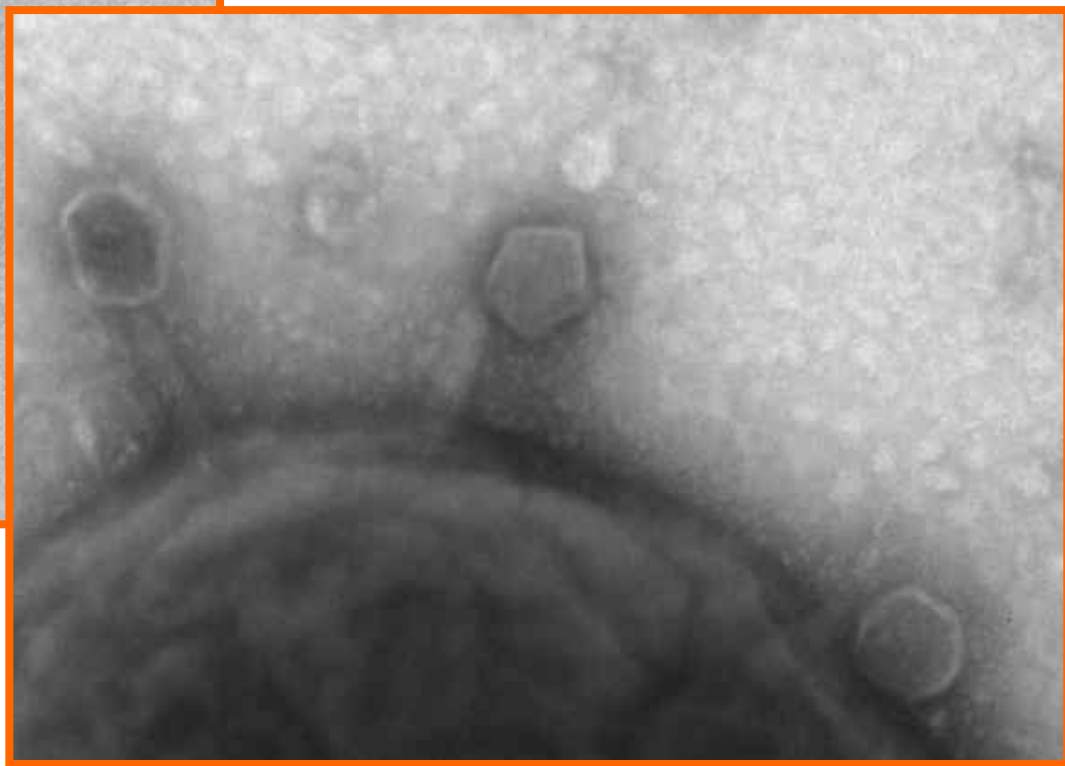
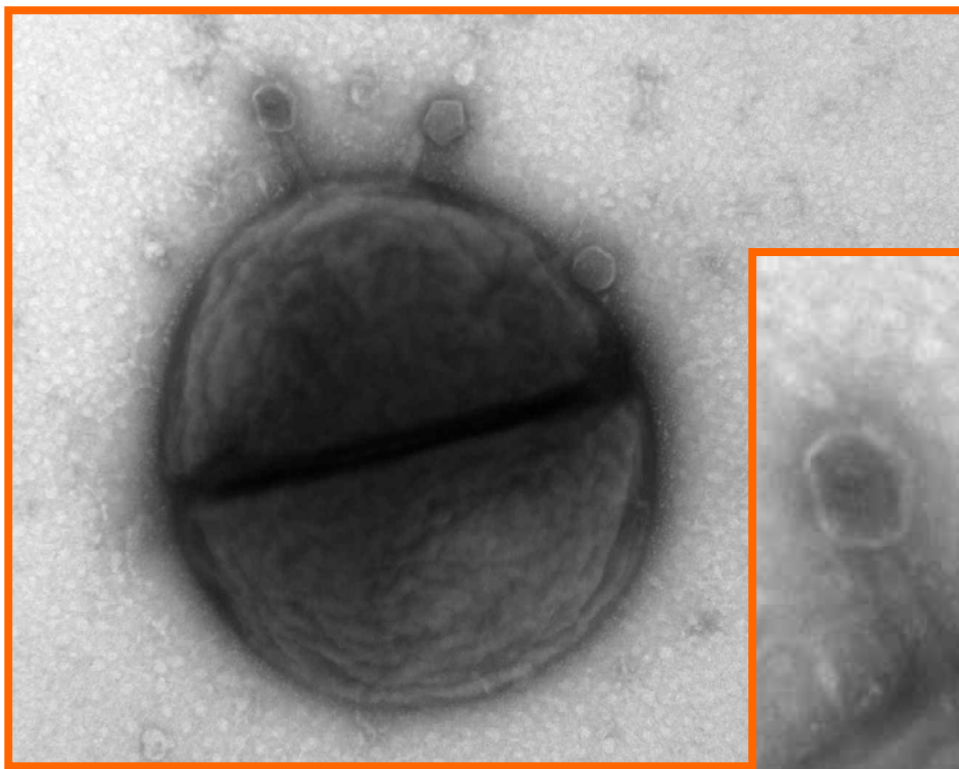
E. coli phage T4 (Myoviridae)



Infection by *E. coli* T4-bacteriophage

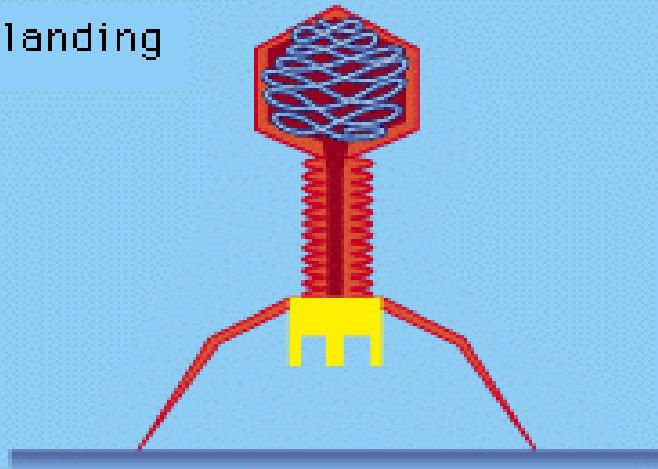


MRSA infection by ISP bacteriophage

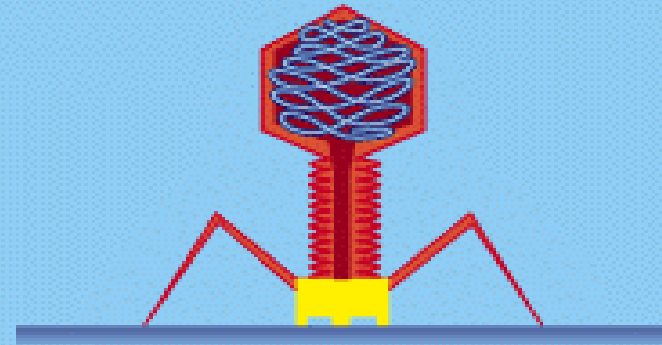


Infection by Myoviridae

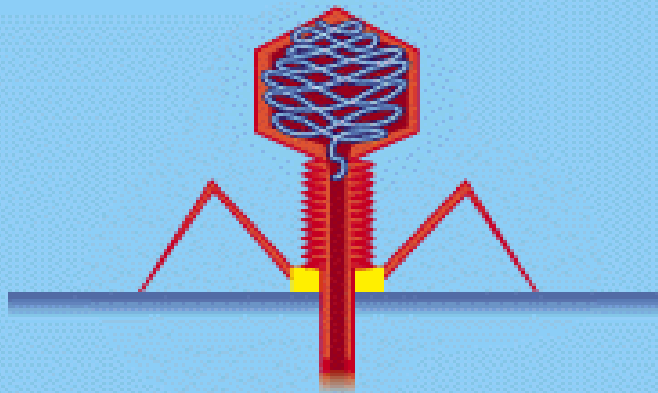
landing



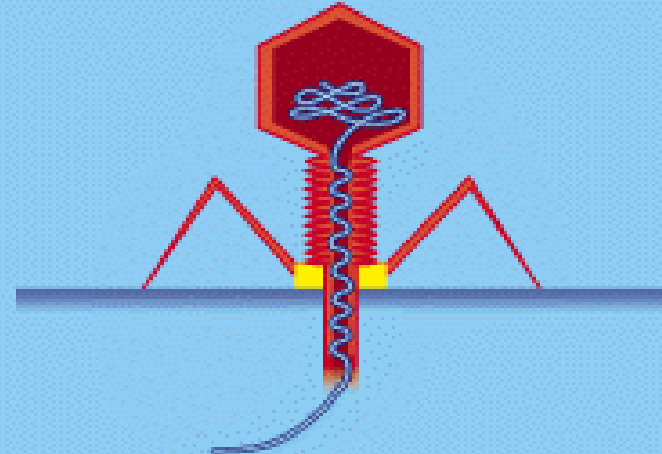
pinning



tail contraction
and penetration

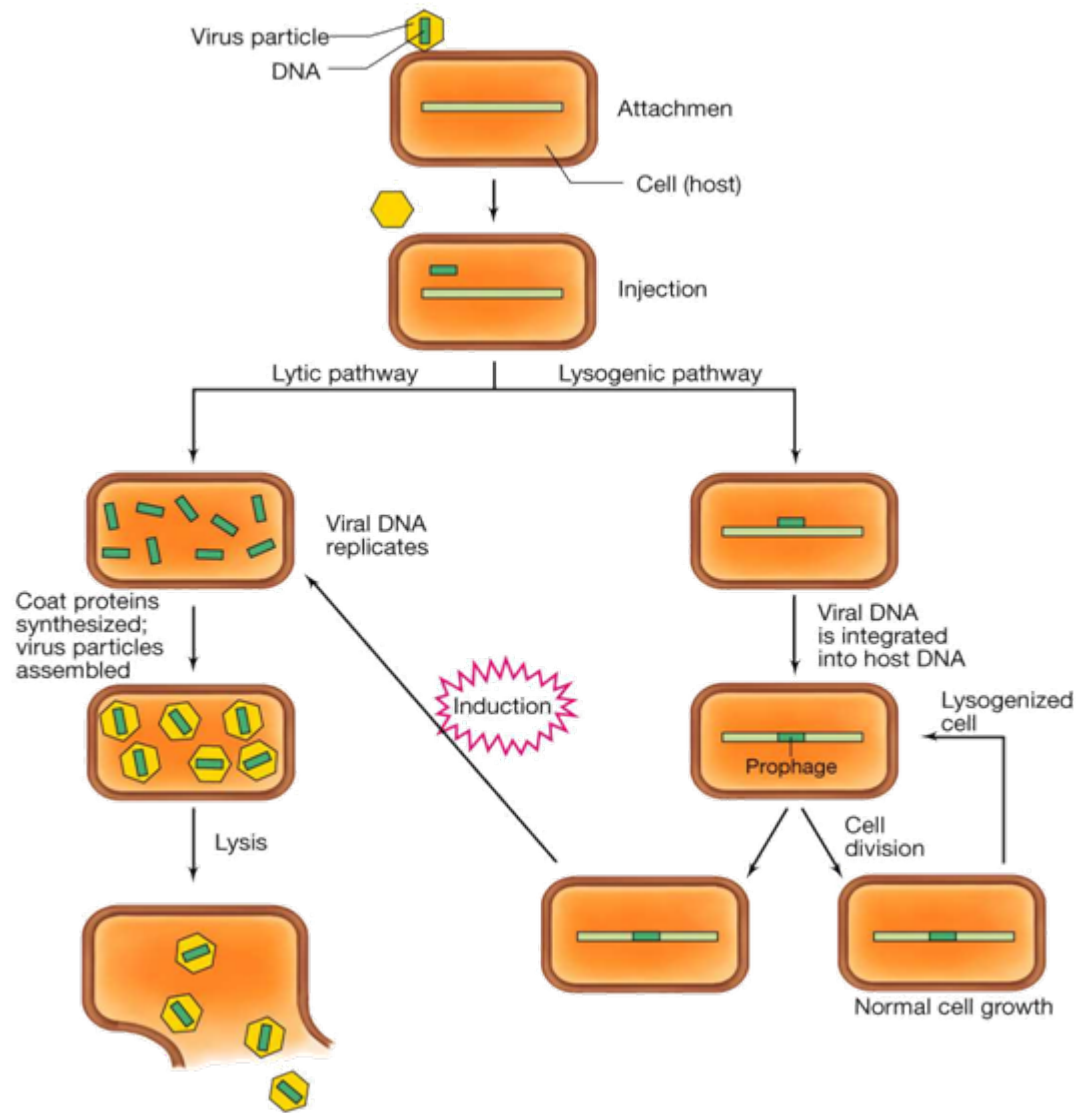


DNA injection



©1994 Encyclopaedia Britannica, Inc.

How phages kill bacteria



Phage therapy ?

Potential alternative to the world wide antibiotic resistance problematic?

- Bacteriophage therapy consists in the application of bacteriophages (“bacteria eaters”, natural enemies of bacteria) for killing bacteria
- Still no eukaryotic infections with phages have been reported
- No phage sequences were detected in the human genome
- Natural controllers and co-evolution

We are living in a sea of phages



- - Estimate total number of tailed phage particles on Earth: $4-6 \times 10^{31}$ = 10-fold of number of prokaryotes (*Bergh. 1989. Nature 340: 467-468*) (*Whitamn et al. 1998. PNAS 95: 6578-6583*)
 - Up to 10^9 phages per ml of surface waters
 - Yet, still no infections with phages have been reported, nor were any phage sequences detected in the human genome

Phages vs. Antibiotics

PHAGE

- Very specific (e.g. part of the strains of one species)
- Development of new phage preparations: relatively easy and inexpensive
- Disease causing agents has to be known (*for now*)
- No known side effects

ANTIBIOTIC

- Non specific (including commensal flora)
- Development of new antibiotics: time-consuming and expensive
- Broad spectrum, agents can be unknown
- Multiple side effects

East vs. West



WEST

Frederic Twort Felix d'Hérelle
UK 1915 France/Canada 1917

"User-friendly" ANTIBIOTICS
1940s - Today

Antibiotic resistance
BWC/QAMH

Stalin WW II

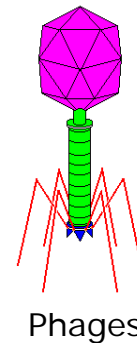
EAST



George Eliava
Georgia, USSR



Eliava Institute, Tbilisi,
Georgia 1923 - Today



Phages



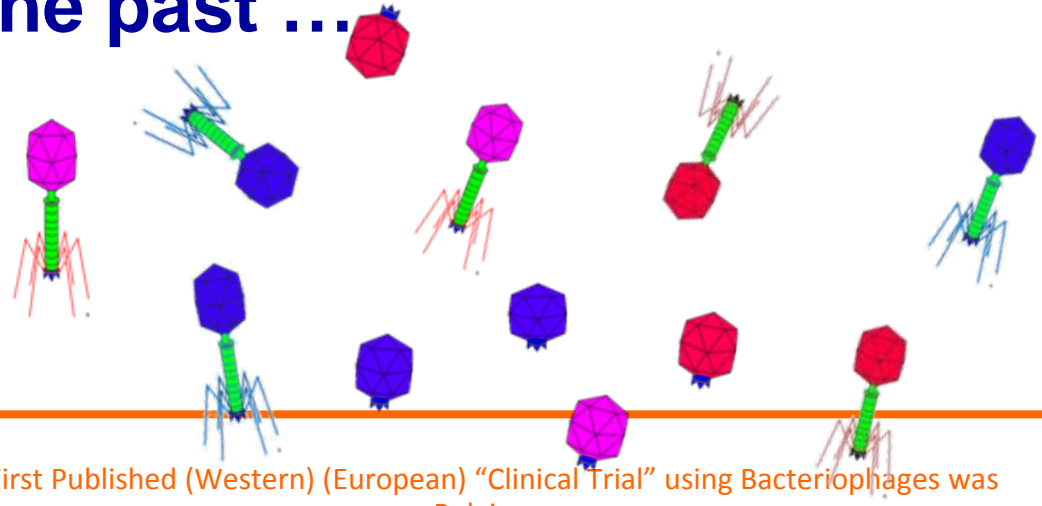
Dr. Maya Merabishvili

The past ...



- Eli Lilly and Company
- Swan Myers (Abbot Laboratories)
- Squibb and sons (B. M. S.)
- Laboratoire Parke-Davis (Pfizer)
- Instituts Pasteur de Paris et de Lyon
- Laboratoire du Bactériophage (5 prep.) (Robert & Carrière)
- German company Antipiol
- Saphal en Suisse
- Ex-URSS (Géorgie –Russie)

The past ...



First Published (Western) (European) "Clinical Trial" using Bacteriophages was Belgian...

Bruynoghe, R. & Maisin J. , 1921

Essais de thérapeutique au moyen du bactériophage du staphylocoque
Institut de bactériologie de l' Université de Louvain
J Compt Rend Soc Biol 85: 1120-1121

- Bacteriophages against Staphylococcus injected into 6 patients with anthrax or abscesses, as close as possible to the infected area
- Reduction of the expansion of the lesions and often total disappearance after 24 to 48 hours

ESSAIS DE THÉRAPEUTIQUE AU MOYEN DU BACTÉRIOPHAGE
DU STAPHYLOCOQUE,
par R. BRUYNOGHE et J. MAISIN.

Nous avons eu l'occasion d'utiliser le Bactériophage du Staphylocoque dans un but thérapeutique et les quelques résultats favorables obtenus nous engagent à les signaler.

Cet essai nous semblait assez logique, étant donné que ces bactériolysats contiennent un principe immédiatement nuisible aux Staphylocoques et l'antigène staphylococcique indispensable à toute vaccination active dont les effets thérapeutiques ne peuvent se manifester que 5 ou 6 jours plus tard.

Dans notre note précédente nous avons vu que le sérum normal du Lapin n'empêche nullement le Bactériophage d'opérer la dissolution de ces microbes. Nous avons pu contrôler également ce fait pour le sérum humain. Dans ce but nous ensemençons des tubes de sérum stérile, d'un côté avec du Staphylocoque, d'un autre côté avec du Bactériophage et du Staphylocoque : l'inhibition sur le développement de ce dernier s'opère comme dans les cultures en bouillon. Il en est de même pour les essais de dissolution de ces cultures déjà développées au moment de l'addition du Bactériophage.

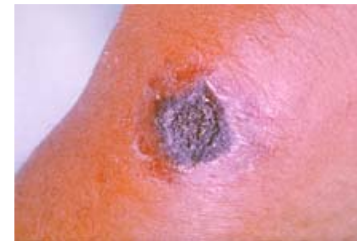
Ce n'est pas ici la place de donner des détails cliniques concernant les malades que nous avons traités et nous nous contentons de signaler que nous avons appliqué cette thérapeutique chez 6 patients atteints d'anthrax ou de furoncles. Nous avons injecté aussi près que possible de la région malade, des doses de bactériolysats (stérilisées par une heure de chauffage à 56°) variant de 0,5 à 2 c.c. L'effet n'a pas tardé à se manifester par la diminution de l'empatement au niveau des lésions et souvent par la disparition totale de ces dernières en 24 à 48 heures. Les infections déjà arrivées à la suppuration se vident et sèchent rapidement.

A la suite de ces inoculations, il se produit, chez certains malades, une ascension fébrile, chez d'autres la température ne subit guère de modification. Il nous a semblé que cette élévation de la température se produit surtout chez ceux atteints de vastes lésions et où la lyse rapide entraîne la résorption de grandes quantités de produits microbiens. L'endroit d'injection est durant 24 heures douloureux et légèrement œdématié.

Nous avons essayé cette thérapeutique chez des patients atteints d'anthrax ou de furoncles, mais il n'est pas impossible que d'autres lésions telles que les acnés et les diverses complications staphylococciques d'autres affections cutanées ne puissent profiter de la même médication.

Ces observations ne sont évidemment pas assez nombreuses pour établir définitivement la valeur de cette méthode et elles n'ont pu être assez prolongées pour déterminer jusqu'à quel point ces inoculations protègent contre les rechutes.

(Institut de bactériologie de l'Université de Louvain).



The past: Phage therapy efficacy

"Vaccination" study in Tbilisi, Georgia (1965)

- Children, aging 6 months to 7 years old
- 17.044 Children ingested bacteriophages against *Shigella dysenteriae*
- 13.725 Children, living at the opposite side of the streets, served as a control group
- Dysentery incidence in control group is 2.6 fold higher than phage treated group

Babalova *et al.* 1968. Preventive value of dried dysentery bacteriophage.
Zh. Mikrobiol. Epidemiol. Immunobiol. 2: 143-145.

Today: Phage applications in the Eliave Phage Therapy Centre, Tbilizi, Georgia



Laboratory of Phage Morphology and Biology,
specialized on phage selection and creation of phage
preparations



Clinical use of phages

- Stone, *Science* (2002)
- Fox, *Nature biotechnology* (2003)
- Merril *et al.*, *Nature reviews* (2003)
- Levin & Bull, *Nature* (2004)
- Projan *et al.*, *Nature biotechnology* (2004)
- Schoolnik *et al.*, *Nature biotechnology* (2004)
- Thiel, *Nature biotechnology* (2004)
- Clark & March, *Trends in biotechnology* (2006)
- Debarbieux *et al.*, *Journal of Infectious Diseases* (2010)

=> FIRST CLINICAL TRIALS

Today: Phage application on a shot wound



Today: Phage applications in Poland, Czech Republic



ul. Rudolfa Weigla 12
53-114 Wrocław
Poland
tel: +48-71-337 1172




sevapharma
Sevapharma, a.s., Průmyslová 1472/11, 102 19 Praha 10, Czech Republic
phone.: +420 296 584 631, +420 296 584 637, fax: +420 267 317 354
obchod@sevapharma.cz
www.sevapharma.cz

“Fishing” for phages



Investment in phage therapy?

- Difficulties in protection through intellectual property rights

Invention



Novel



industrially
applicable

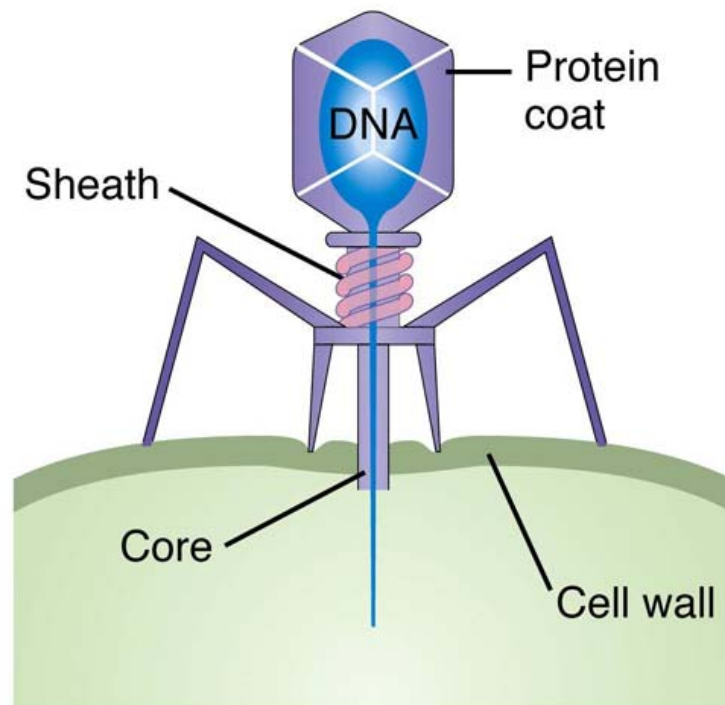
Is a Phage an invention?

- = technical creation
- = technical solution for a technical problem
- patents granted for inventions in *all* areas of technology



Is a Phage an invention?

- Natural phages vs manipulated phages



Investment in phage therapy?

- Importance of regulatory frame with exclusivities for the investor

Regulatory Hurdles 2007

European regulatory conundrum of phage therapy

*Gilbert Verbeken,
Daniel De Vos[†],
Mario Vaneechoutte,
Maya Merabishvili,
Martin Zizi &
Jean-Paul Pirnay*

*[†]Author for correspondence
Hospital Center of the Base –
Queen Astrid, Laboratory for
Molecular & Cellular
Technology, Burn Unit,*

The treatment of infectious diseases with antibiotics is becoming increasingly challenging. Very few new antimicrobials are in the pharmaceutical industry pipeline. One of the potential alternatives for antibiotics is phage therapy. Major obstacles for the clinical application of bacteriophages are a false perception of viruses as 'enemies of life' and the lack of a specific frame for phage therapy in the current Medicinal Product Regulation. Short-term borderline solutions under the responsibility of a Medical Ethical Committee and/or under the umbrella of the Declaration of Helsinki are emerging. As a long-term solution, however, we suggest the creation of a specific section for phage therapy under the Advanced Therapy Medicinal Product Regulation.

- No specific frame for phage therapy in the current Medicinal Product Regulation
- Actually EMA classification as “Biological” under discussion
- One option: “Medical Ethical Committee”
- Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

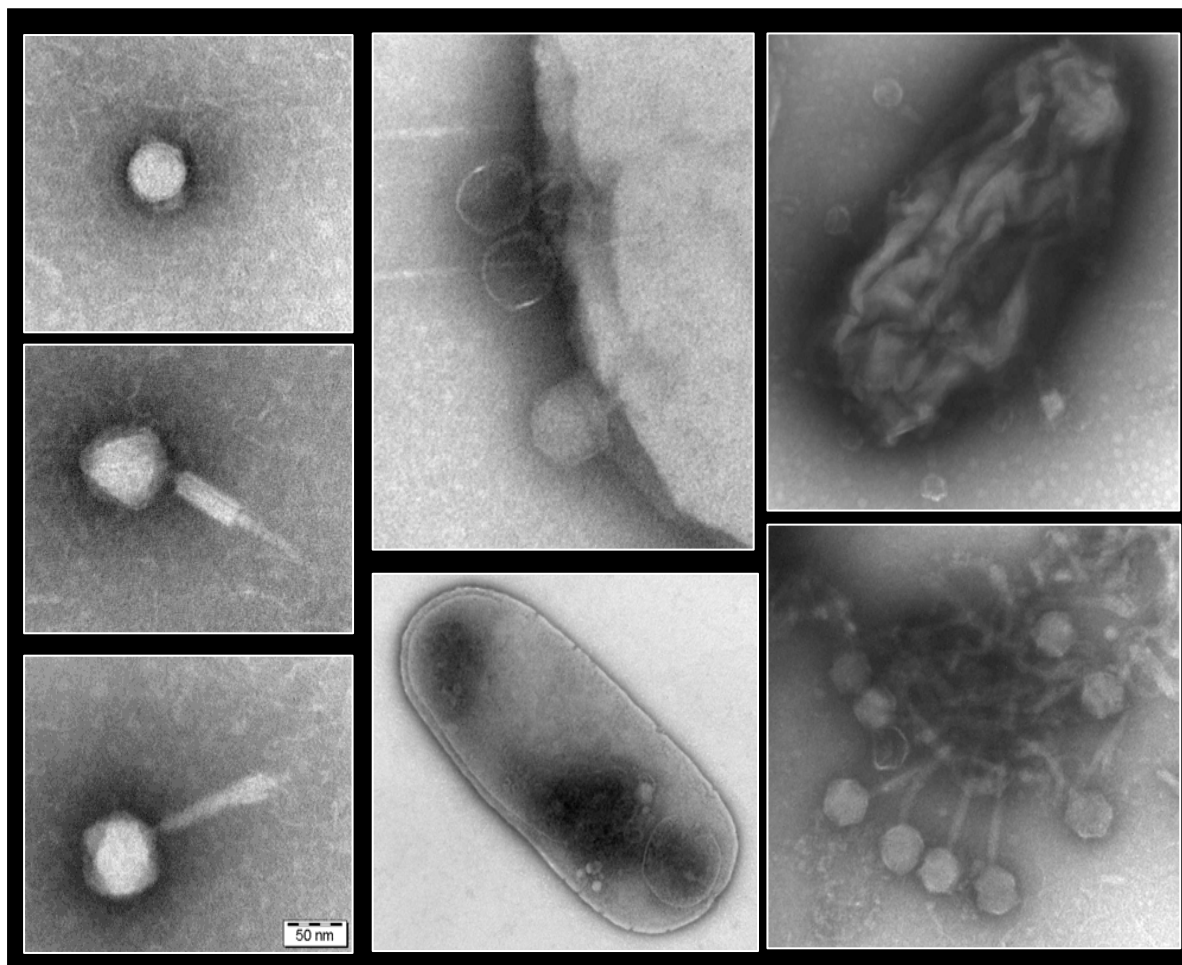
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by ... 59th WMA General Assembly, Seoul, October 2008

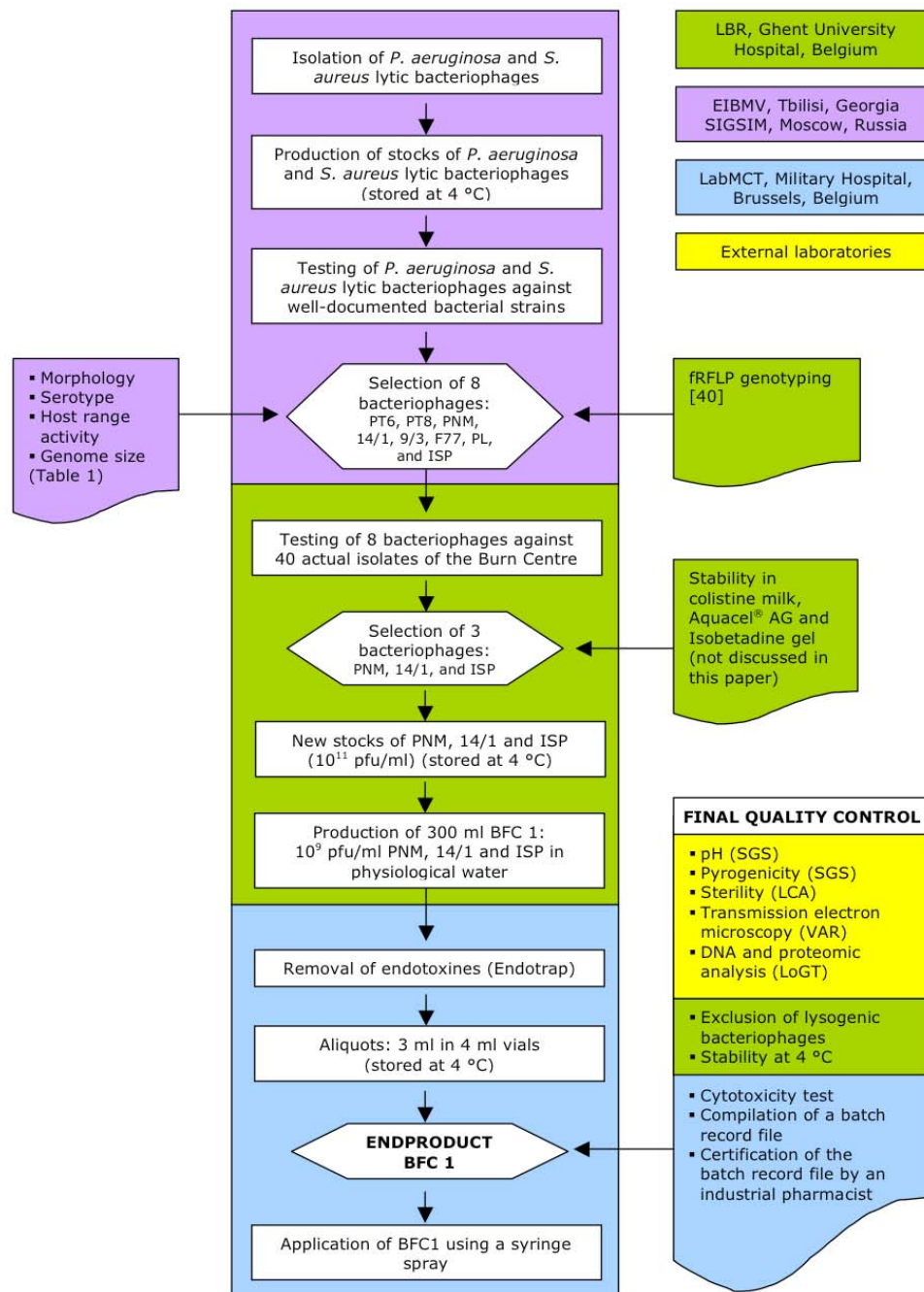
35.

In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

BFC 1



Quality controlled (small scale) phage production



- Lack of well-defined, quality-controlled phage preparations
- Often inadequate matching of bacteria and phages (empirically)
- Endotoxins in crude phage preparations
- “GMP-like” production

OPEN ACCESS Freely available online



Quality-Controlled Small-Scale Production of a Well-Defined Bacteriophage Cocktail for Use in Human Clinical Trials

Maya Merabishvili^{1,2,8}, Jean-Paul Pirnay^{2*}, Gilbert Verbeken², Nina Chanishvili¹, Marina Tediashvili¹, Nino Lashkhi¹, Thea Glonti¹, Victor Krylov³, Jan Mast⁴, Luc Van Parys⁵, Rob Lavigne⁶, Guido Volckaert⁶, Wesley Mattheus⁶, Gunther Verween², Peter De Corte², Thomas Rose², Serge Jennes², Martin Zizi^{5,7}, Daniel De Vos², Mario Vanechoutte⁸

¹ Elava Institute of Bacteriophage, Microbiology and Virology (EBMV), Tbilisi, Georgia, ² Laboratory for Molecular and Cellular Technology (LabMCT), Burn Centre, Queen Astrid Military Hospital, Bruynstraat, Neder-over-Heembeek, Brussels, Belgium, ³ Laboratory of Bacteriophage Genetics, State Institute for Genetics and Selection of Industrial Microorganisms (SIGSIM), Moscow, Russia, ⁴ Unit Electron Microscopy, Veterinary and Agricultural Research Centre (VAR), Ukkel, Brussels, Belgium, ⁵ Section Health of the Division Well-Being (Belgian Defence Staff), Queen Astrid Military Hospital, Neder-over-Heembeek, Brussels, Belgium, ⁶ Laboratory of Gene Technology (LoGT), Katholieke Universiteit Leuven, Leuven, Belgium, ⁷ Department of Physiology (FYSP), Vrije Universiteit Brussel, Jette Brussels, Belgium, ⁸ Laboratory of Bacteriology Research (LBR), Ghent University Hospital, Ghent, Belgium

Ethical approval study > 28/06/'07



Universitair Ziekenhuis Brussel



Vrije Universiteit Brussel

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Brussel, 28 juni 2007

Ons Kenmerk 2007/007

BEKRACHTIGING ADVIES VAN DE COMMISSIE MEDISCHE ETHIEK

Betreft : project voor experiment getiteld

Evaluatie van BCF 1, een cocktail van drie lytische bacteriofagen, voor de behandeling van brandwonden geïnfecteerd met bijzonder resistente stammen voor de bacteriën *Pseudomonas aeruginosa* en/of *Staphylococcus aureus*
Protocol VUB dd 01/09/2007

Op datum van 20-06-2007 gaf de voorzitter van de Commissie Medische Ethiek een **GUNSTIG ADVIES** aan bovenvermeld project voor experiment bij mensen.

DIT ADVIES WORDT VANDAAG BEKRACHTIGD DOOR DE AANWEZIGE LEDEN (zie lijst in bijlage)

Deze goedkeuring blijft geldig voor de duur van het project. De Commissie wenst een jaarlijks overzicht van de stand van zaken van het project te ontvangen. De studieresultaten dienen overgemaakt te worden aan de Commissie bij het beëindigen van de studie. Zij herinneren de verantwoordelijke van het experiment eraan dat dit experiment onder zijn persoonlijke verantwoordelijkheid zal worden uitgevoerd. Het gunstig advies van de Commissie betekent geenszins dat de Commissie de verantwoordelijkheid van het experiment op zich neemt. De Commissie Medische Ethiek werkt en is georganiseerd volgens de richtlijnen van GCP.

Met de meeste hoogachting,

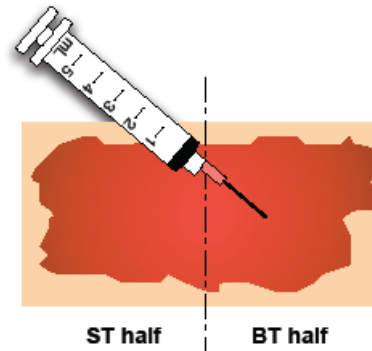
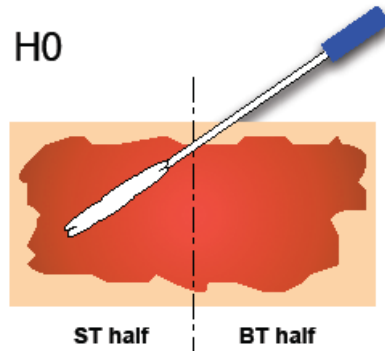
P. Devroey, voorzitter

CC: FAGG, Departement R&D, t.a.v. Mevr. Musch Eurostation blok 2, Victor Hortaplein 40 / 40 - 1060 Brussel



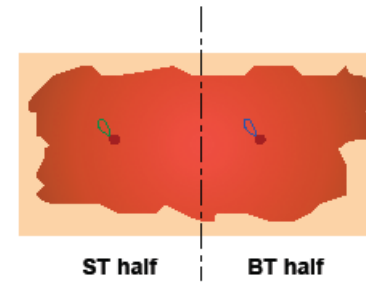
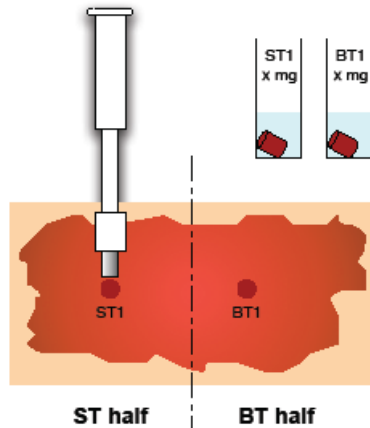
BACTERIOPHAGE COCKTAIL STUDY (2007/007) PROCEDURES
(ADDENDUM TO CRF)

H0



1.
 - a) Divide the wound into two halves.
ST: "Standard Treatment".
BT: "Bacteriophage Treatment".
 - b) Take a swab sample of the two halves.
 - c) Label the swabs (Patient name + ST0 or BT0).
 - d) Send them to the Bacteriology Lab.

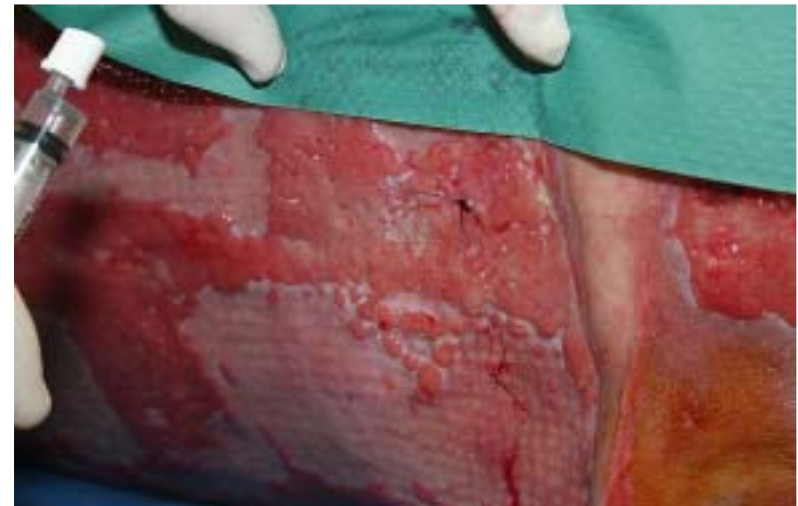
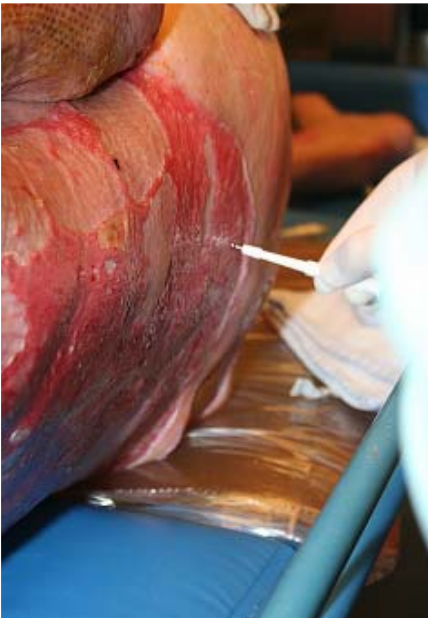
2.
 - a) Apply a local anaesthetic (Xylocaine 2%).



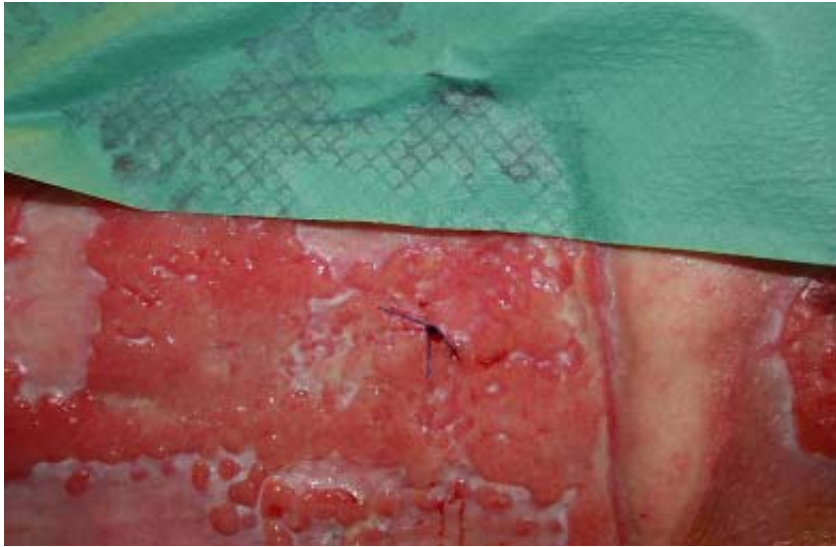
3.
 - a) Take two 2 mm punch biopsy samples.
 - b) Weigh the two biopsies.
 - c) Place them into two sterile labelled recipients with 0.5 ml PBS buffer (LabMCT).

4.
 - a) Suture the two punch biopsy wounds with a different-colored wire.

Patient treatment



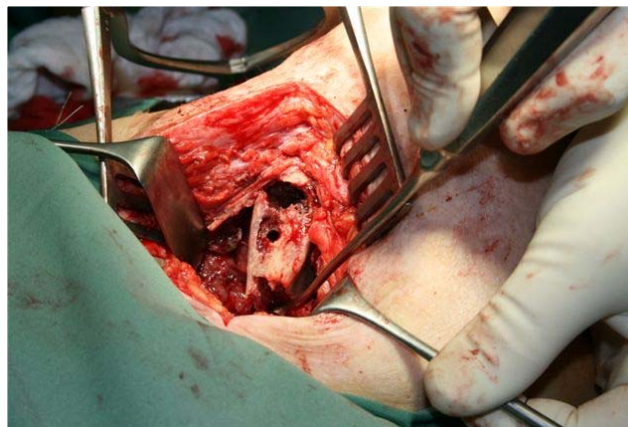
Patient treatment



(First) (Western) (Belgian) Burn Wound Trial, 2007-2010



“Declaration of Helsinki”



“Declaration of Helsinki”



“Declaration of Helsinki”



ANNEX 1 Directive 2001/83/EC (Medicinal Products for Human Use)

Part I: Standardized marketing authorisation dossier

Part II: Specific marketing authorisation dossier

- Well-established medicinal use
- Essentially similar medicinal products
- Additional data required in specific situations
- Similar biological medicinal products
- Fixed combination medicinal products
- Documentation for applications in exceptional circumstances
- Mixed marketing authorisation applications

Part III: Particular medicinal products

- Biological medicinal products
 - Plasma-derived medicinal products
 - Vaccines
- Radio-pharmaceuticals and precursors
 - Radio-pharmaceuticals
 - Radio-pharmaceutical precursors for radio-labelling purposes
- Homeopathic medicinal products
- Herbal medicinal products
- Orphan medicinal products

Part IV: Advanced Therapy Medicinal Products

- Gene therapy medicinal products
- Somatic cell therapy medicinal products
- Tissue engineered products
- Combined advanced therapy medicinal products

Parliamentary Questions - 14 February 2011

- E-001144/2011

Question for written answer to the Commission
Rule 117

Ivo Belet (PPE) and Catherine Trautmann (S&D)

Subject: Bacteriophage therapy

- Bacteriophages are the natural enemies of bacteria. Bacteriophages are always present where bacteria are.
- Bacteriophages exclusively reproduce within bacterial cells, destroying them. Bacteriophages never infect human cells. For each specific bacterium, a specific bacteriophage exists.
- Scientific publications demonstrate the safety of bacteriophages for human therapeutic use.
- Bacteriophage therapy is applied today in e.g. some former Soviet Republics (e.g. Russia, Georgia).
- Bacteriophage therapy is used to complement or as an alternative to antibiotic therapy. This alternative is important when antibiotics fail.
- Bacteriophage therapy is important as an extra tool in the battle against bacteria resistant to the currently available antibiotics. This problem is, in Europe as elsewhere, seriously increasing.
- Today's European medicinal product regulatory framework (Commission Directive 2003/63/EC — Consolidated) does not define specific requirements related to bacteriophage therapy.
- Can the Commission explain how bacteriophage therapy would be regulated today, within Europe?
- If bacteriophage therapy were regulated as a classical, *not* bacteriophage-specific, 'chemical', 'particular' or 'advanced' medicinal product, which legal framework would apply for patients who need bacteriophage therapy today?
- How could the current European medicinal product regulatory framework be optimised with the aim of the European introduction of bacteriophage therapy?
- Would the Commission consider creating an extra documentation box 'Bacteriophage Therapy' in the section regulating 'Particular Medicinal Products' (Part III of Commission Directive 2003/63/EC) ?

Answer to the Parliament - 29 March 2011

- E-001144/2011

Answer given by Mr Dalli * on behalf of the Commission

- The EU's legislation on medicinal products does not define specific requirements related to bacteriophage therapy or medicines composed of bacteriophages.
- Bacteriophages could be regulated as any other medicinal product if the product fulfils the definition of a medicinal product, namely:
 - any substance or combination of substances presented as having properties for treating or preventing disease in human beings
 - or
 - any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.
- The classification of any given product as a medicinal product is performed by the Member States taking into account all the characteristics of the product. When a product is classified as a medicinal product, such product may be placed on the EU market only after a marketing authorisation for such product has been delivered. In order to obtain a marketing authorisation, an application which meets the requirements laid down in Directive 2001/83/EC, as amended, has to be submitted. If the active substance is a biological substance that is produced by or extracted from a biological source, then specific requirements are required in the marketing authorisation dossier and are defined in Directive 2001/83/EC Annex I, Part III.
- In addition, if the product is based on genes (gene therapy), cells (cell therapy) or tissues (tissue engineering), the medicinal product is eligible as an advanced therapy medicinal product. In such cases, specific rules as established in Regulation (EC) No 1394/2007 apply. All data shall allow the competent authority to draw a conclusion on the quality, efficacy and safety of the product and the positive benefit/risk balance for the patients. The product is then authorised to be placed on the market.
- The Commission considers that the existing regulatory framework as explained above is adequate for bacteriophage therapy without the need for an extra set of documentation for bacteriophage therapy.

European Medicines Agency (EMA) Innovation Task Force (ITF)

The **Innovation Task Force (ITF)** is a multidisciplinary group that includes scientific, regulatory and legal competences, set up to ensure Agency-wide coordination in the areas of interest and to provide a forum for early dialogue with applicants.

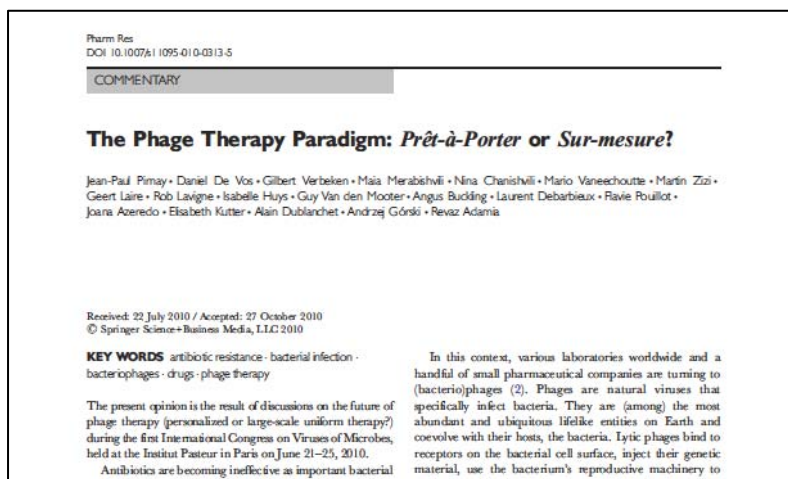
Briefing meetings

- The scope of the briefing meetings covers regulatory, technical and scientific issues arising from innovative medicines development, new technologies and borderline products.
- The ITF, within 60 days of receipt of a valid request from an applicant, arranges free-of-charge briefing meetings to facilitate the informal exchange of information and the provision of guidance early in the development process.
- The scientific discussions are led by experts from the Agency network, working parties and committees, where the best available scientific expertise is represented.
- Briefing meetings are meant to complement and reinforce existing formal regulatory procedures (e.g. ATMP classification, ATMP certification, designation of orphan medicinal products, CHMP scientific advice, etc).

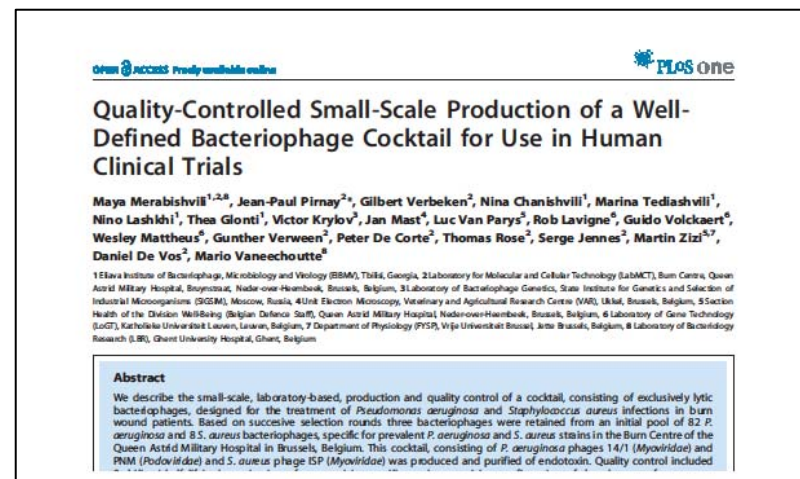
Briefing Documents ITF



Future Microbiology, October 2007

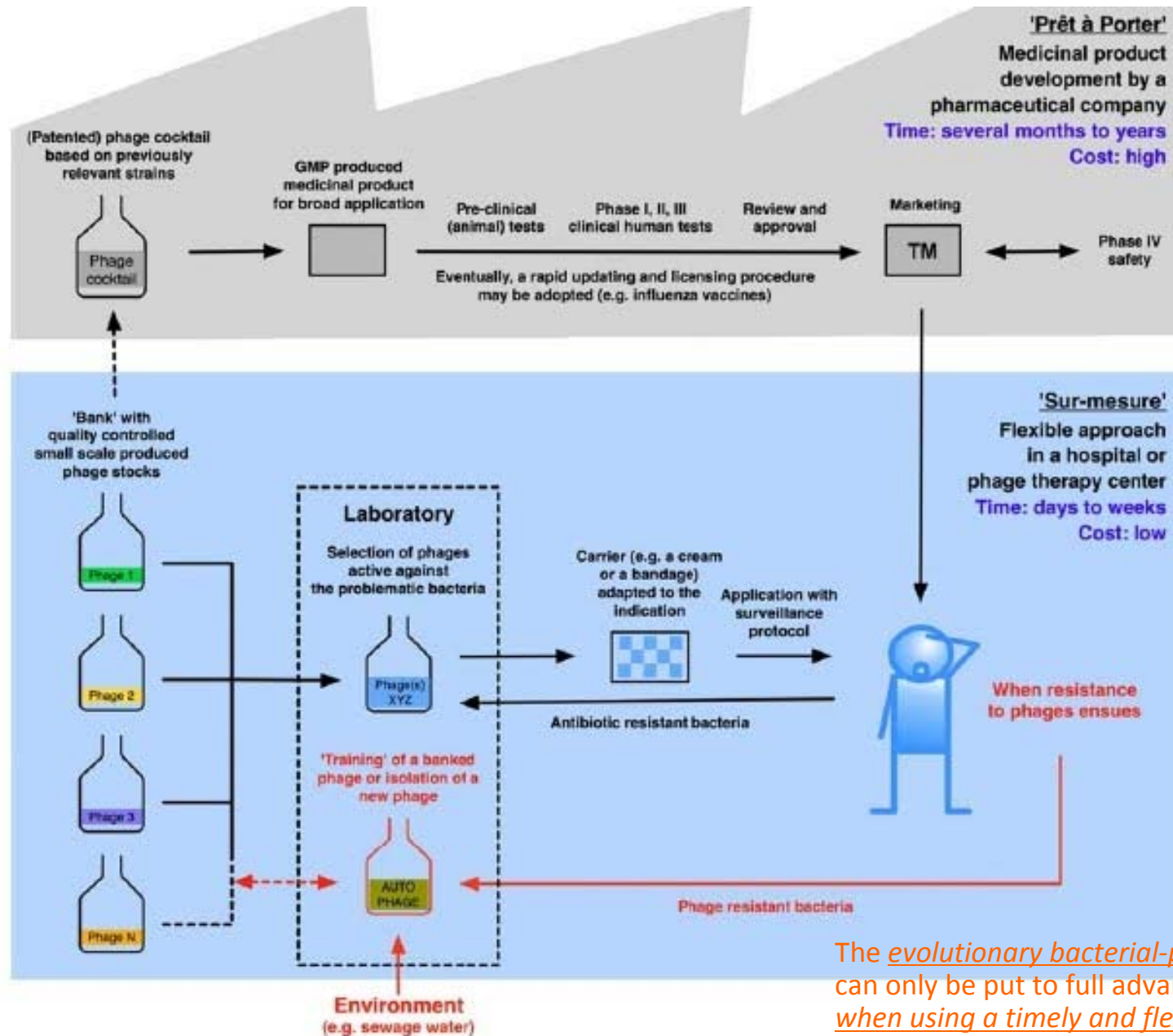


Pharm Res, November 2010



PloS ONE, March 2009

'Prêt-à-porter' vs 'Sur-mesure'



ITF Opinions

- For sure a natural bacteriophage is a biological
- Requirements have to be discussed case-by-case, individually
- Quality slide of presentation is part of a full IMPD dossier
- Full documentation package is needed for final evaluation
- Phages are not the only evolving products
 - There are precedents, e.g. stem cell preparations
 - Cell cultures for autologous grafting are also precedents
 - There is also the precedent of the flu vaccine

ANNEX 1 Directive 2001/83/EC (Medicinal Products for Human Use)

Part I: Standardized marketing authorisation dossier

Part II: Specific marketing authorisation dossier

- Well-established medicinal use _____ < Bacteriophage Therapy M.P.
- Essentially similar medicinal products
- Additional data required in specific situations
- Similar biological medicinal products
- Fixed combination medicinal products
- Documentation for applications in exceptional circumstances
- Mixed marketing authorisation applications

Part III: Particular medicinal products

- Biological medicinal products _____ < Bacteriophage Therapy M.P.
 - Plasma-derived medicinal products
 - Vaccines
- Radio-pharmaceuticals and precursors
 - Radio-pharmaceuticals
 - Radio-pharmaceutical precursors for radio-labelling purposes
- Homeopathic medicinal products
- Herbal medicinal products
- Orphan medicinal products

Part IV: Advanced Therapy Medicinal Products _____ < Bacteriophage Therapy M.P.

- Gene therapy medicinal products
- Somatic cell therapy medicinal products
- Tissue engineered products
- Combined advanced therapy medicinal products

Conclusions

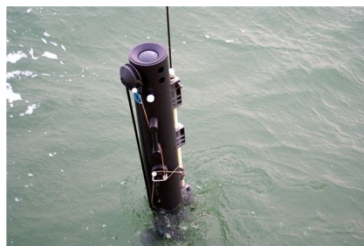
- Things are moving at the European and Member State level
- EMA knows what natural phages, used as therapeutics, are
- Regulators apply regulation, they do not change regulation
- There is an important role for MD's using (or wanting to use) natural phages and patient groups at the level of sensitizing politicians so that European Regulatory framework can be adapted 'bottom-up'
- Why not creating a totally new framework for phage therapy?
Next to the "medicinal product" regulatory framework, next to the "medical device" regulatory framework, next to the "human cell and tissue" regulatory framework, ... ?

P.H.A.G.E.



P-H-A-G-E.org

° July 16, 2009
www.P-H-A-G-E.org



Thanks to:
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We will be happy to answer any question...



Slides are available on <http://www.facm.ucl.ac.be> → Lectures