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*Where should we look next  
for antimicrobial therapy?*

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Jon Cohen

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*The Diseases and Casualties this Week,*



Abortive	5	Imposthume	11
Aged	43	Infants	6
Ague	2	Killed by a fall from the Bo-	1
Apoplexie	1	frey at Alhal'ows the Great	1
Bleeding	2	Kingevil	2
Burnt in his Bed by a Candle	1	Lethargy	1
at St. Giles Cripplegate	1	Pallie	1
Canker	1	Plague	7165
Childbed	4	Rickets	17
Chirifomes	18	Rising at the Lights	11
Consumption	134	Scouring	5
Convulsion	6	Scurvy	2
Cough	2	Spleen	1
Dropic	35	Spotted Feavers	101
Feaver	309	Stuborn	17
Flox and Small-pox	5	Stone	2
Frighted	3	Stopping of the stomach	9
Gowt	1	Strangury	1
Grief	1	Suddeny	1
Gripping in the Guts	51	Serient	49
Jandies	1	Teeth	121
		Thrill	5
		Timpany	1
		Tifick	11
		Vomiting	3
		Winde	3
		Wormes	15

Plague  
7165

Spotted  
feaver  
101

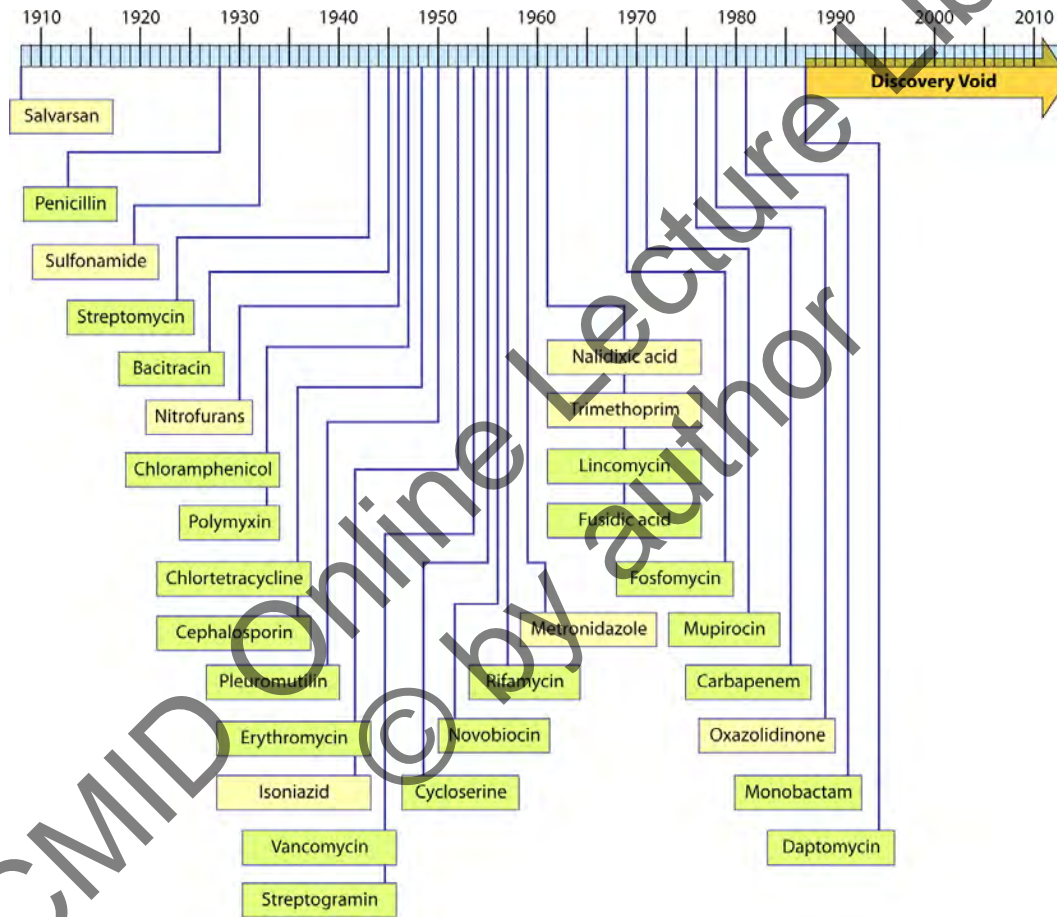
Feaver 309

Christned	{ Males — 495 } { Females — 421 } { In all — 916 }	Buried	{ Males — 4095 } { Females — 4202 } { In all — 8297 }	Plague	7165
Increased in the Burials this Week		607			
Parishes clear of the Plague		4	Parishes Infected	126	

*The Assize of Bread set forth by Order of the Lord Mayor and Court of Aldermen,  
A penny Wheaten Loaf to contain Nine Ounces and a half, and three  
half-penny White Loaves the like weight.*

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Illustration of the “discovery void.” Dates indicated are those of reported initial discovery or patent.



Silver L L Clin. Microbiol. Rev. 2011;24:71-109

## Specific measures to control antibiotic use

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- Formulary selection
- Rapid clinical micro information
- Selective antibiotic reporting
- Education
- Computer-based decision assistance
- Restricted pharmaceutical marketing
- Formulary restriction

## What else can we do?

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- **Re-discover forgotten antibiotics**
  - nafcillin
  - fusidic acid
  - mecillinam
  - pristinamycin
  - thiamphenicol
  - fosfomicin
  - spectinomycin

## *What else can we do?*

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- Re-discover forgotten antibiotics
  - Identify new bacterial targets, develop new chemical entities
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## *What else can we do?*

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- Re-discover forgotten antibiotics
  - Identify new bacterial targets, develop new chemical entities
  - **Inhibitors of bacterial pathogenesis/virulence**
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# Inhibitors of bacterial pathogenesis or virulence – some examples

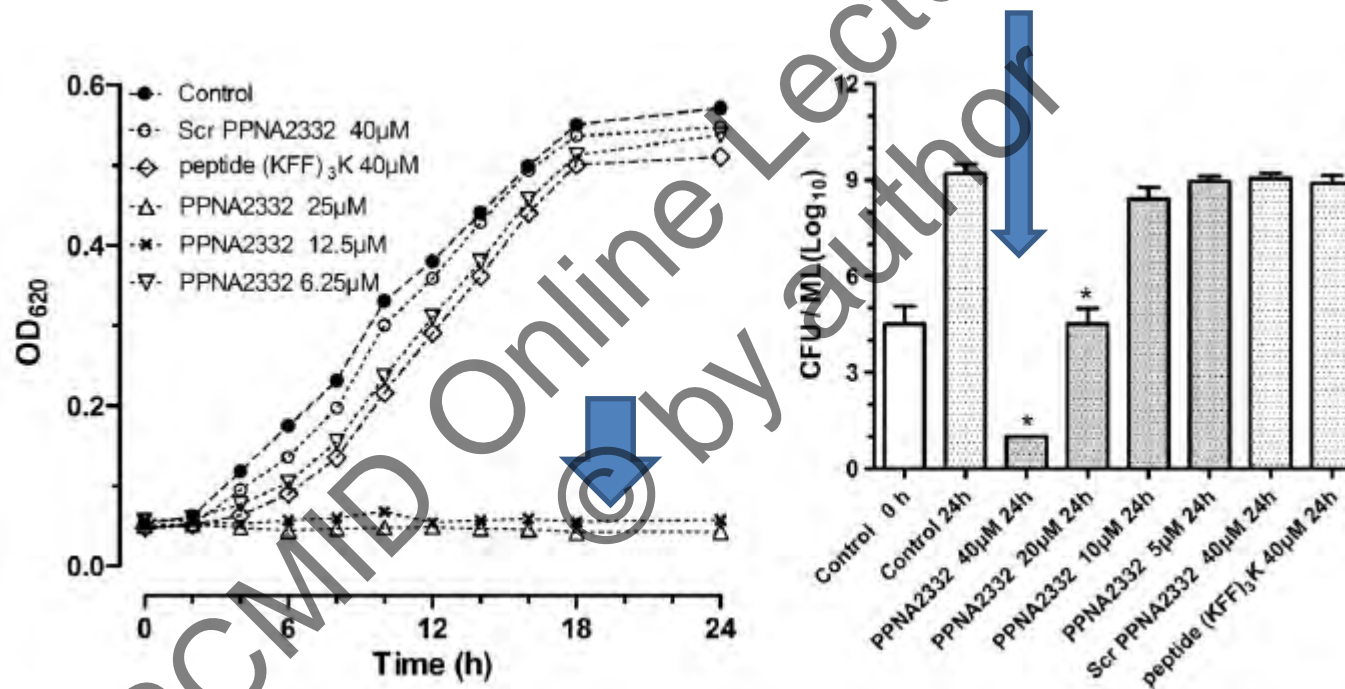
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- **ANTISENSE ANTIBACTERIALS:** short synthetic DNA analogues that inhibit essential gene expression at mRNA level. Can work by inducing cell death or by restoring antibiotic susceptibility.
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# Targeting RNA Polymerase Primary $\sigma^{70}$ as a Therapeutic Strategy against Methicillin-Resistant *Staphylococcus aureus* by Antisense Peptide Nucleic Acid

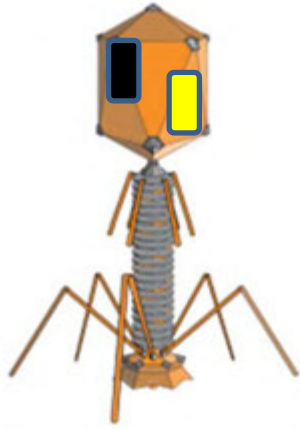
Hui Bai<sup>1,2,3</sup>, Guojun Sang<sup>1</sup>, Yu You<sup>4</sup>, Xiaoyan Xue<sup>1</sup>, Ying Zhou<sup>1</sup>, Zheng Hou<sup>1</sup>, Jingru Meng<sup>1</sup>, Xiaoxing Luo<sup>1\*</sup>





# Inhibitors of bacterial pathogenesis or virulence – some examples

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- ANTISENSE ANTIBACTERIALS: short synthetic DNA analogues that inhibit essential gene expression at mRNA level. Can work by inducing cell death or by restoring antibiotic susceptibility.
  - PHAGE “THERAPY”: reversing bacterial resistance by phage-mediated delivery of dominant sensitive genes. Rather than treating patients, the idea is to use this method to reduce the prevalence of Res<sup>t</sup> bacteria in the environment
-



Phage contains dom ab-sens gene  and tellurite res gene 

MDR bacteria  
In the environment

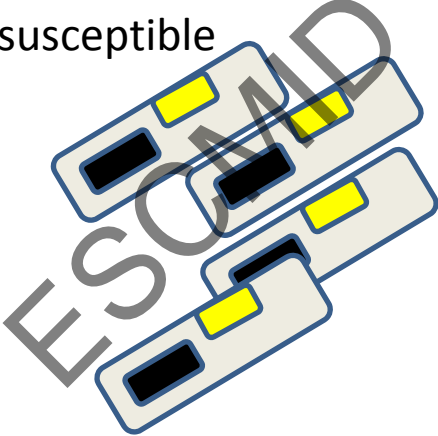


Infected patient  
Can be treated

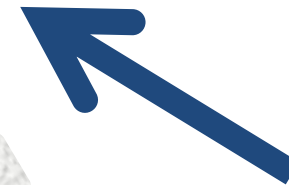
Lysogeny



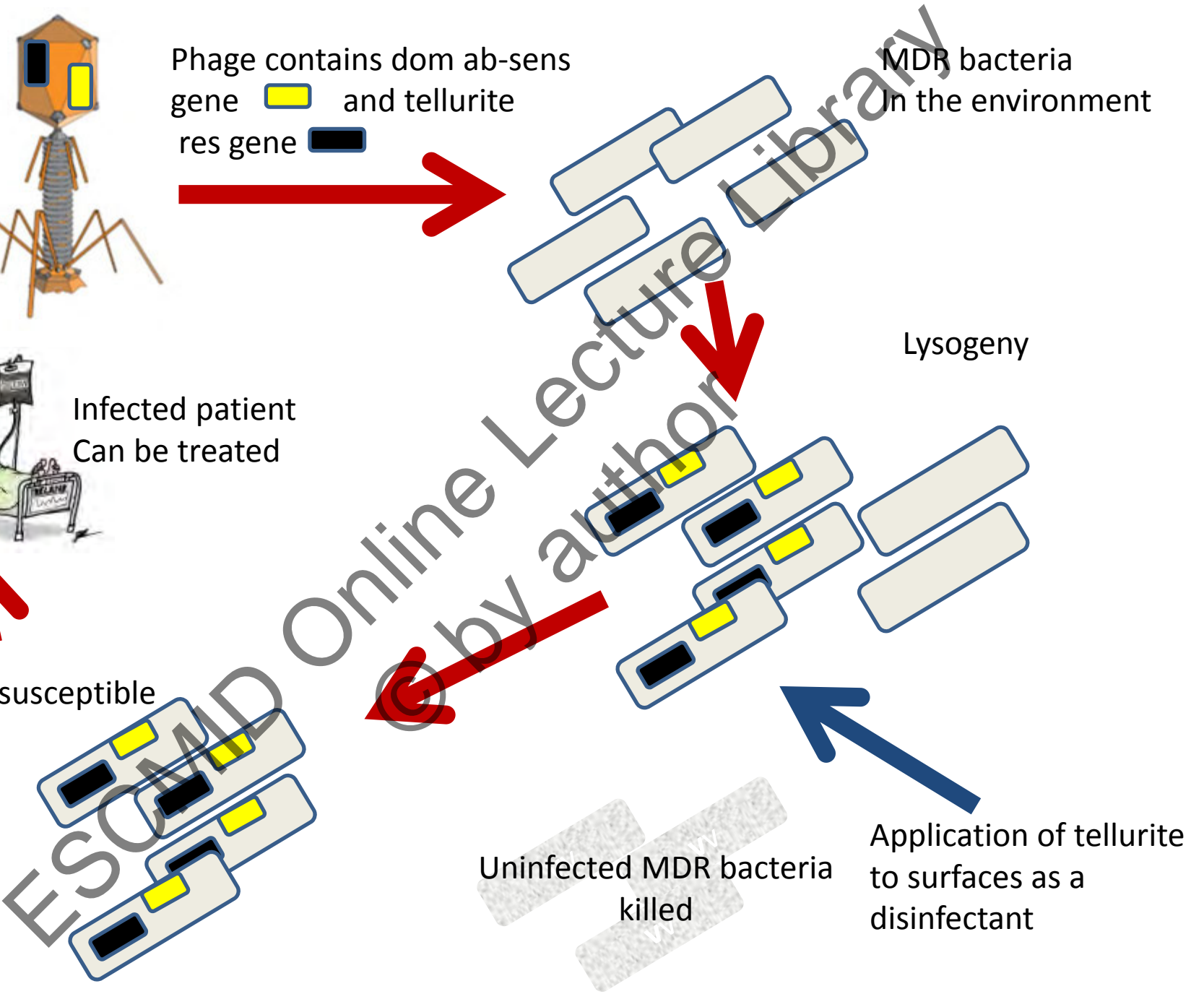
Antibiotic susceptible  
bacteria  
survive



Uninfected MDR bacteria  
killed



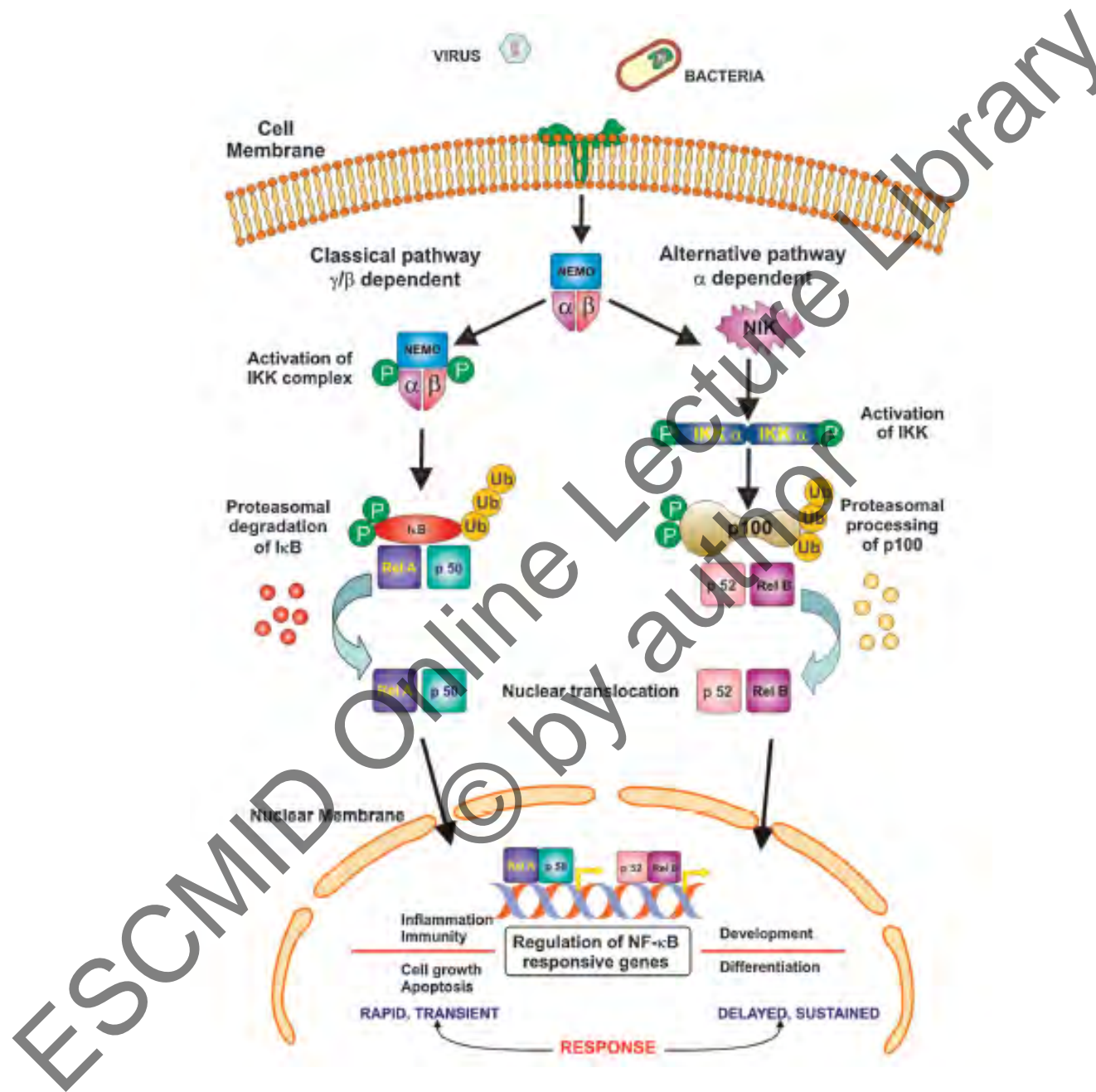
Application of tellurite  
to surfaces as a  
disinfectant

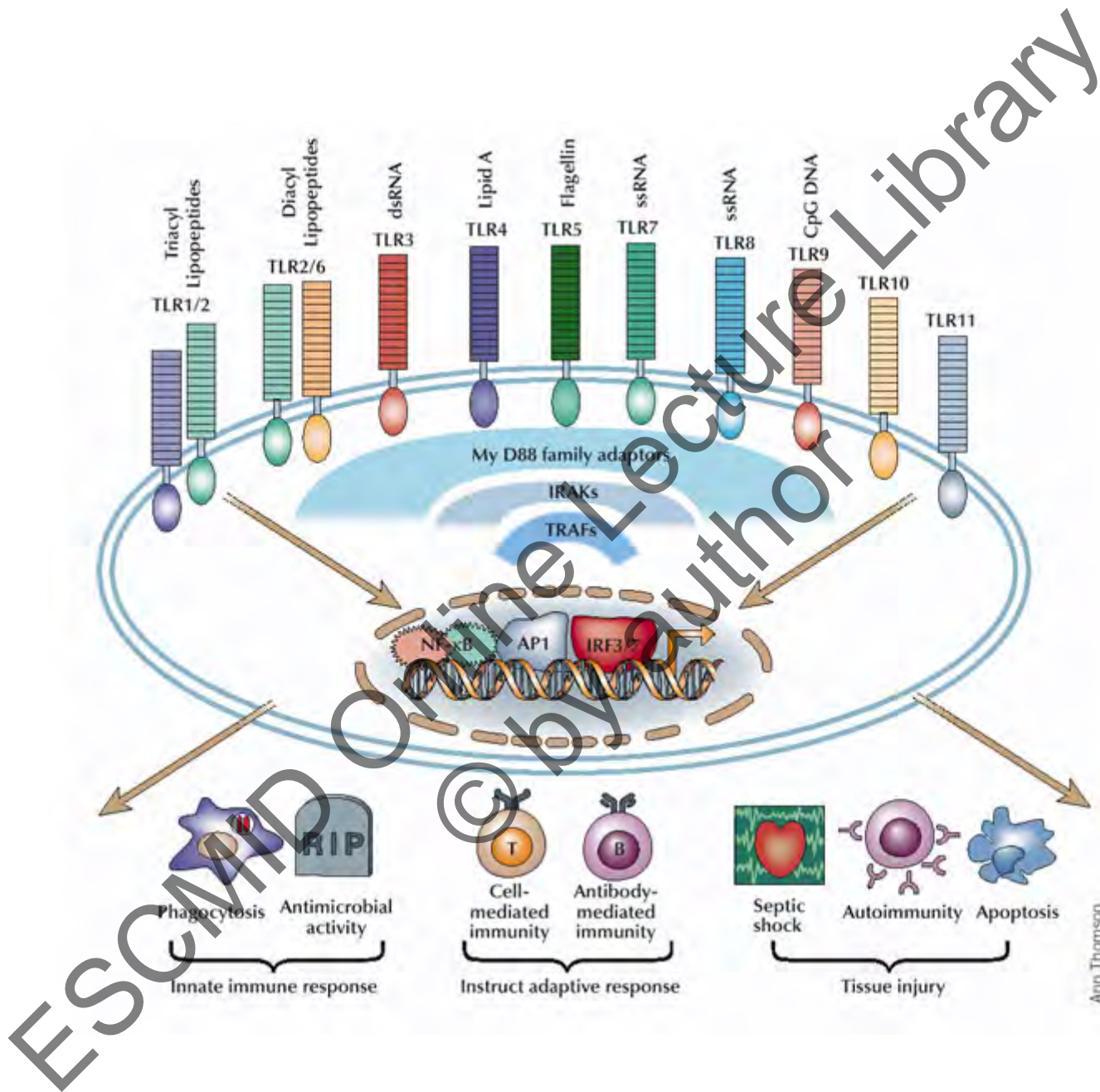


## *What else can we do?*

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- Re-discover forgotten antibiotics
  - Identify new bacterial targets, develop new chemical entities
  - Inhibitors of bacterial pathogenesis/virulence
  - **Modify the host response**
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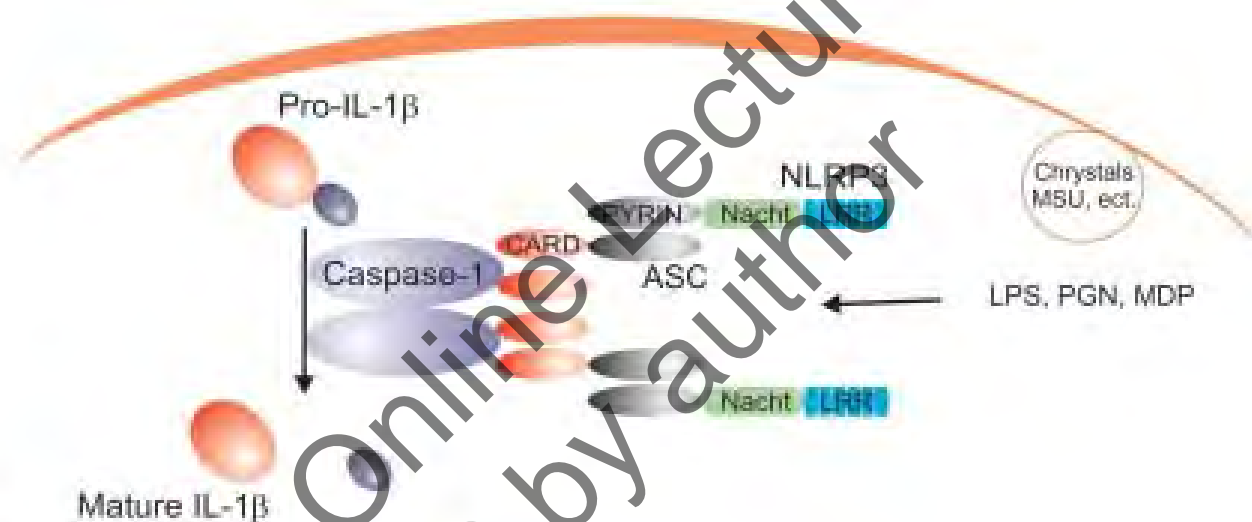




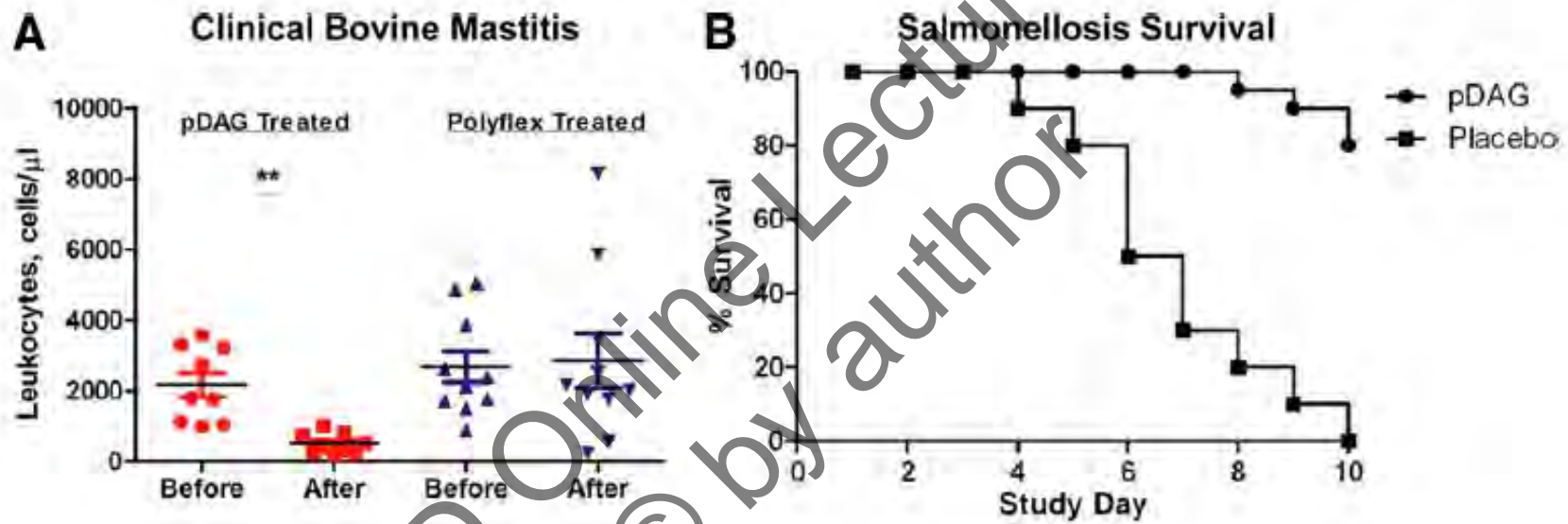
Modlin & Cheng, Nature Med 2004 10:1173

Arno Thomson

# The NLRP3 [NALP3] Inflammasome

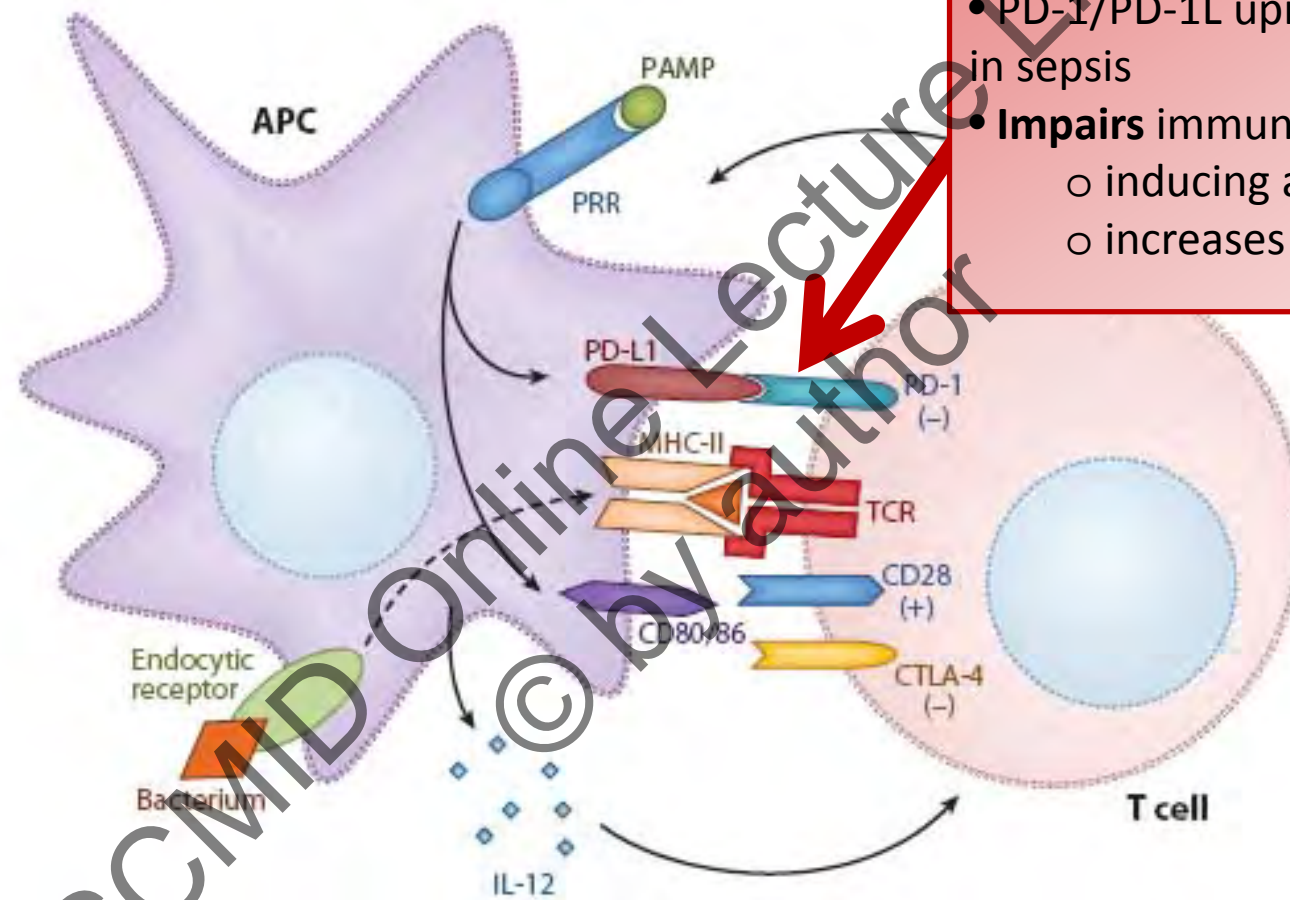


# A New Molecular Entity that induces the NLRP3 inflammasome has broad-spectrum antibacterial effects



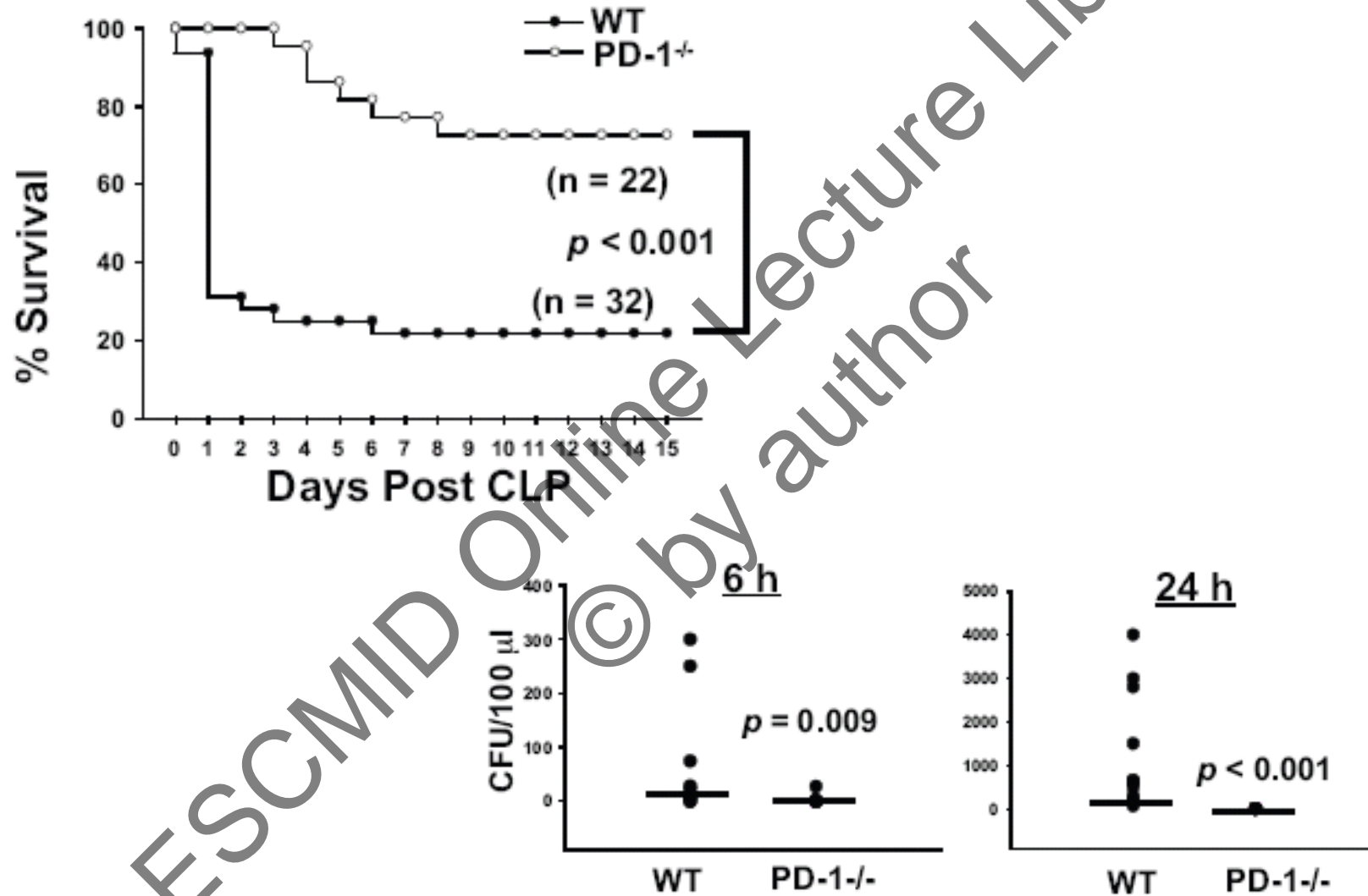


# PD-1: a negative co-stimulatory molecule



- PD-1/PD-1L upregulated in sepsis
- **Impairs** immunity by:
  - inducing apoptosis
  - increases IL-10

# PD-1 on macrophages influences bacterial clearance and survival in a mouse CLP model



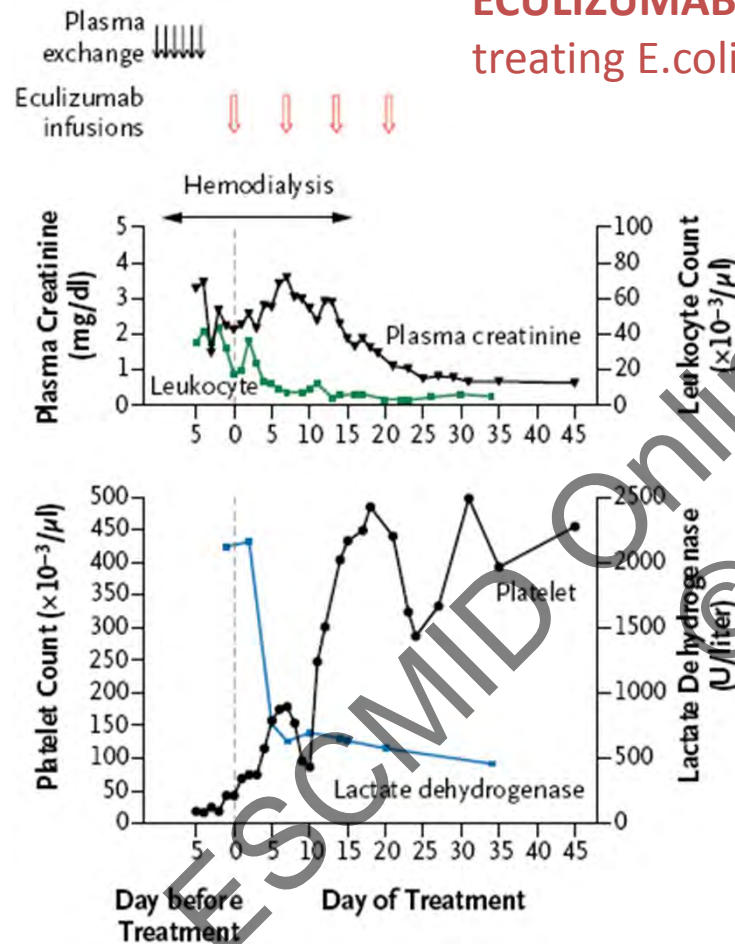
# Adjunctive use of IL-12 with antibiotics to prevent experimental wound infection

*Rat model of fracture-associated Staph aureus infection treated prophylactically with ip ampicillin +/- percutaneous IL-12*

	INFECTION RATE %			
	Day 6	Day 10	Day 14	Day 21
Control	100	100	100	100
Percut IL-12	83	83	100	100
Antibiotic	40	25	0	0
Ab + IL-12	0			0

## Two recent examples of the use of specific Mab's as adjunctive agents for serious infection

**ECULIZUMAB:** An anti complement C5 Mab for treating E.coli STEC-HUS



**PANOBAUMAB:** An IgM anti *P.aeruginosa* O11 LPS for nosocomial pneumonia

**Table 3.** Efficacy of panobacumab in the safety, ITT, PK and PP populations

Parameter	Safety (n=18)	ITT (n=17)	PK (n=17)	PP (n=13)
Overall patient survival at 30 days/ end of study	15 (83.3%)	14 (82.4%)	15 (88.2%)	13 (100%)
Clinical outcome				
resolution	11 (61.1%)	11 (64.7%)	11 (64.7%)	11 (84.6%)
recurrence	2 (11.1%)	2 (11.7%)	2 (11.7%)	2 (15.4%)
continuation <sup>a</sup>	5 (27.8%)	4 (23.5%)	4 (23.5%)	0 (0%)



# Infection and Chronic Disease

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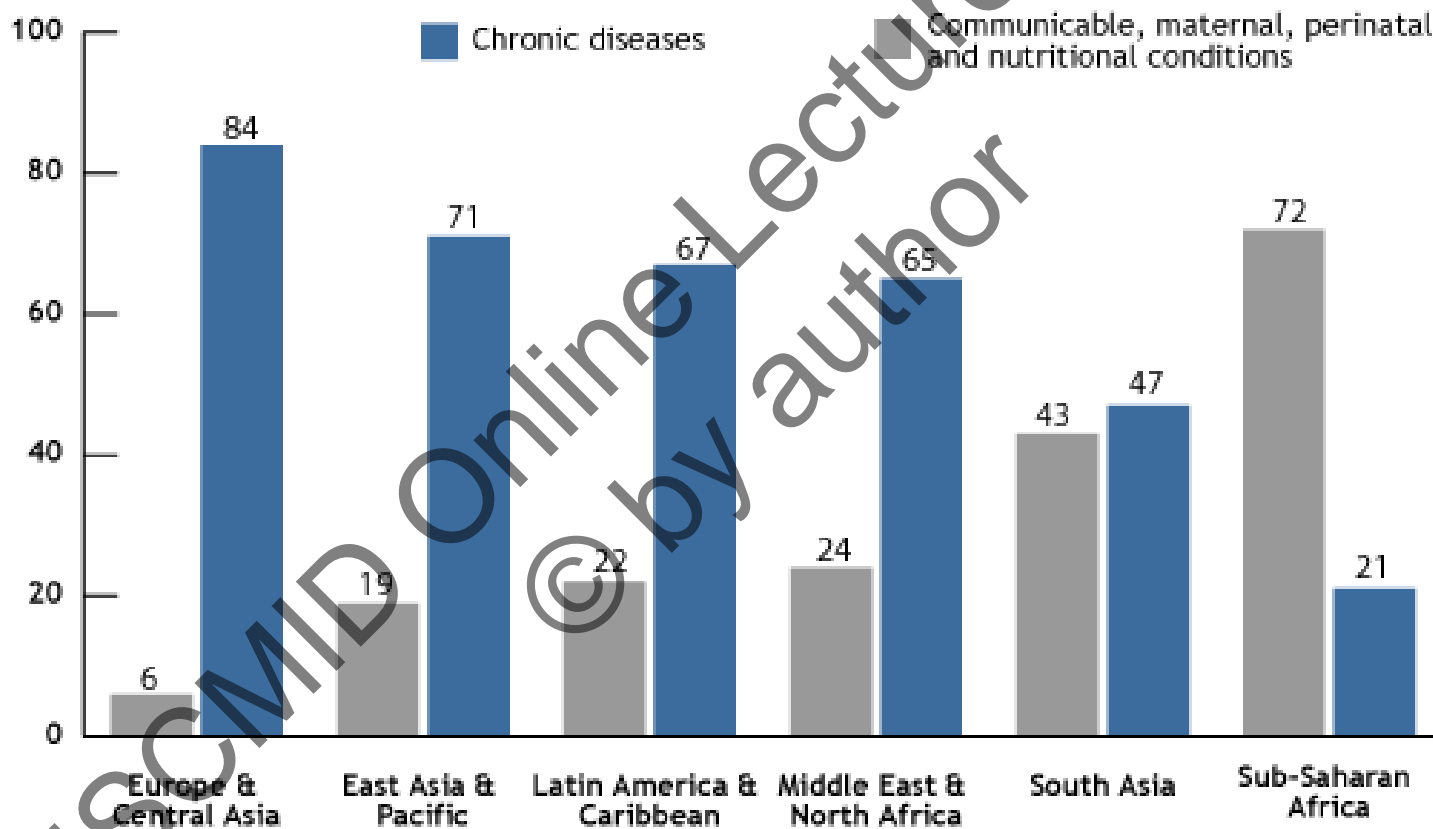
- Peptic ulcer disease *Helicobacter*
  - Autoimmune disease *Hepatitis*
  - Cancer *EBV, HTLV-1*
  - Atherosclerosis *Chlamydia ?*
-

## Diseases in which micro-organisms have been suggested, but not proven, to play a role

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- Kawasaki disease
  - Kikuchi's disease
  - Inflammatory bowel disease/Crohn's
  - Chronic fatigue syndromes
    - "chronic neuroborreliosis"
    - "candida syndrome"
  - Multiple sclerosis
  - Sarcoidosis
-

# The burden of chronic diseases: the new challenge



Colin et al. WHO, 2003



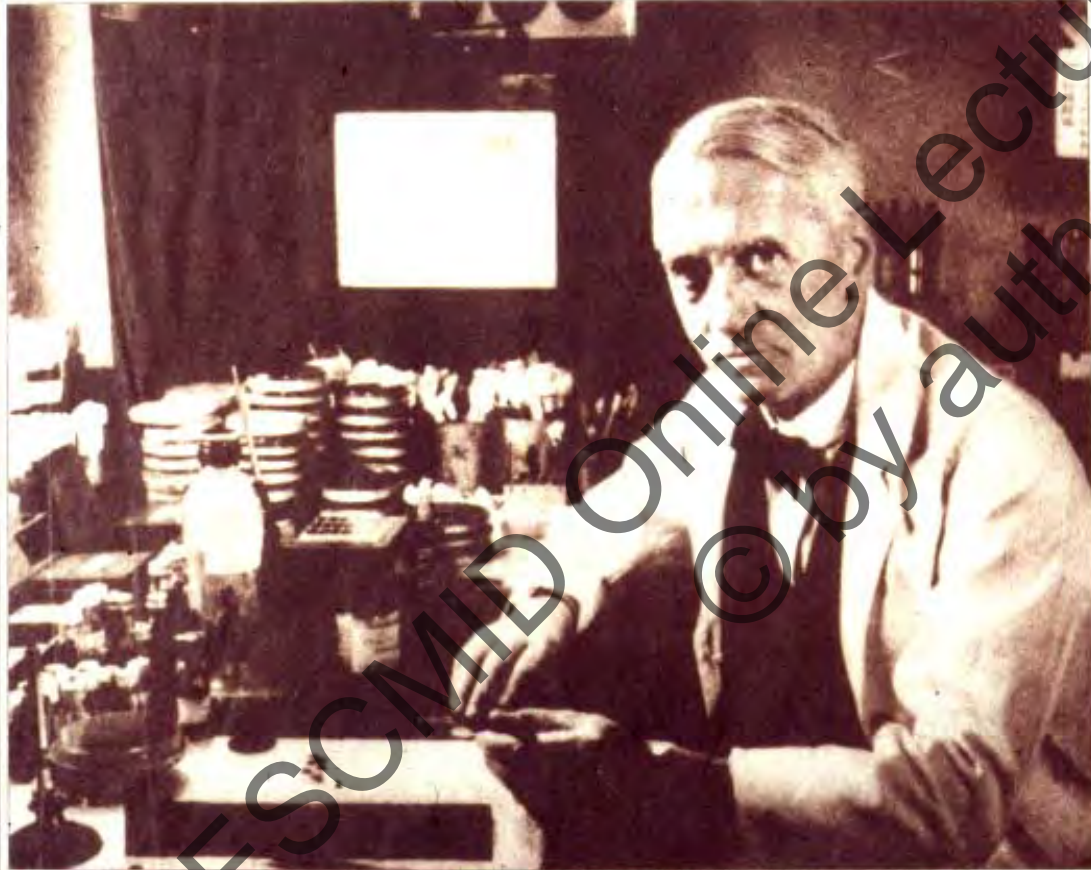
# THE INDEPENDENT

1991 \*\*\*

TUESDAY 21 MAY 1996

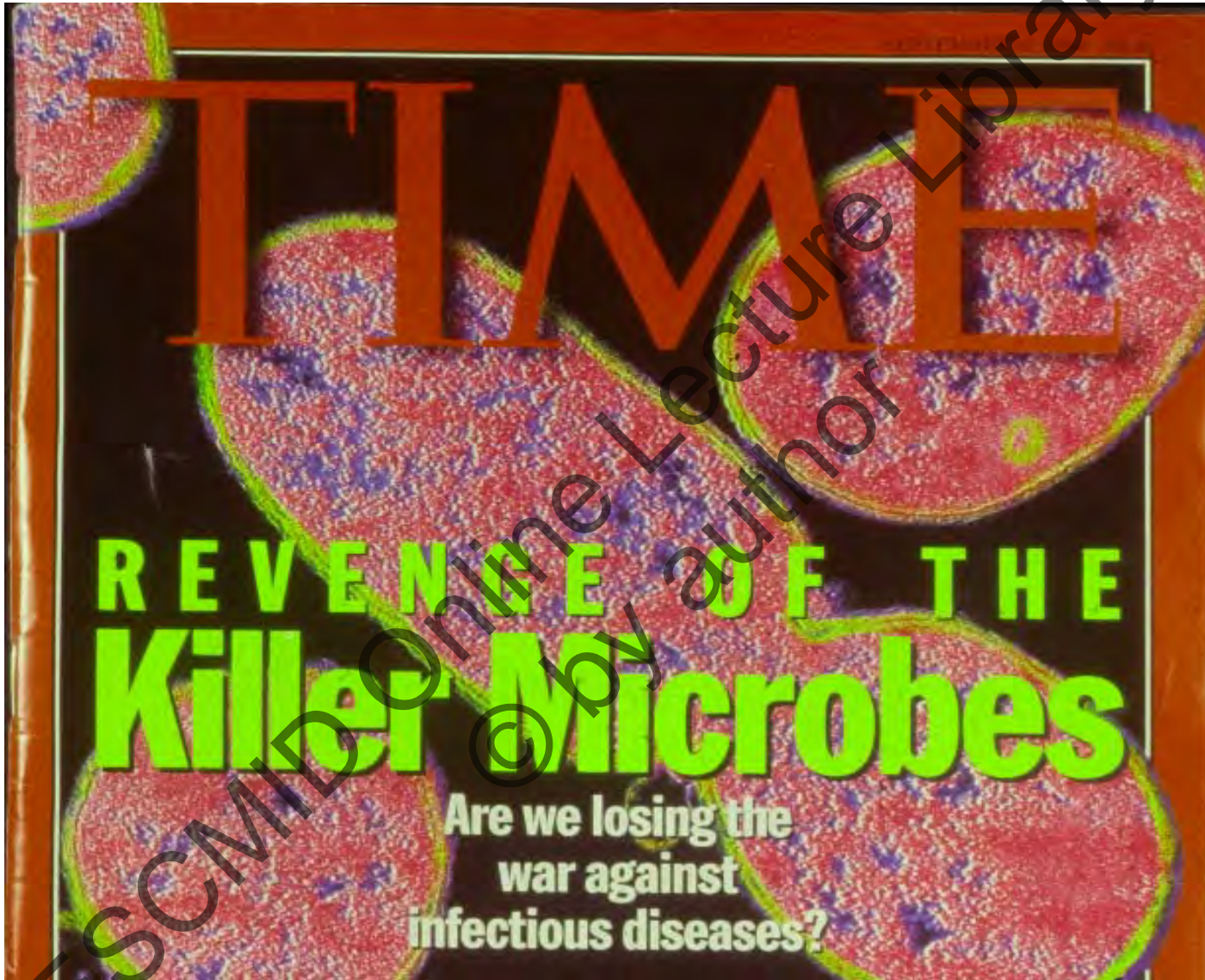
WEATHER Cool and unsettled with sun and showers 40p (34 45p)

## The waning of the antibiotic age



Miracle cure: Alexander Fleming, discoverer of penicillin, in his laboratory in London. In 1945 he was awarded a Nobel Prize for his work on the drug

Scientists call for stricter controls as 'cure-all' loses power



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