

Immunotherapies for Infectious diseases

Bacterial GAPDH as a target to prevent bacterial infections



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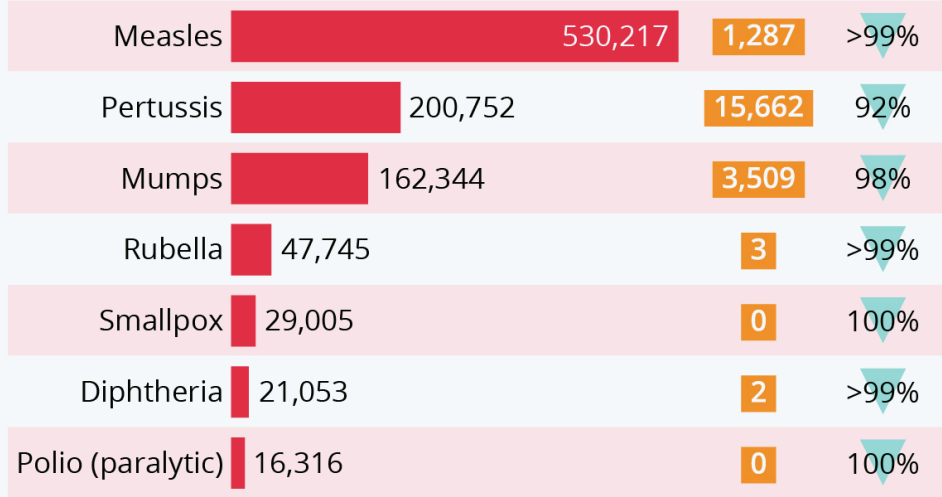


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How Vaccines Eradicated Common Diseases

Annual 20th century morbidity and 2019 morbidity of selected diseases in the U.S.

■ 20th Century Annual Morbidity ■ Reported Cases in 2019 ▼ Percentage Decrease

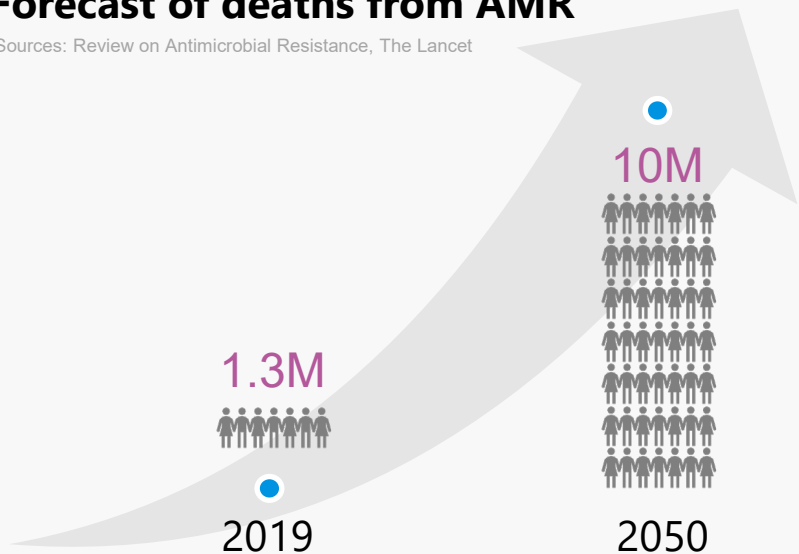


Source: Centers for Disease Control and Prevention



Forecast of deaths from AMR

Sources: Review on Antimicrobial Resistance, The Lancet



Bacteria	Antibiotic Resistance	CDC Hazard	Vaccine available
<i>Escherichia coli</i>	Significant	Urgent	No
<i>Klebsiella pneumoniae</i>	Significant	Urgent	No
<i>Staphylococcus aureus</i> (MRSA)	Significant	Serious	No
<i>Streptococcus pneumoniae</i>	Significant	Serious	Yes (partial) *
<i>Streptococcus agalactiae</i> **	Moderate	Concerning	No

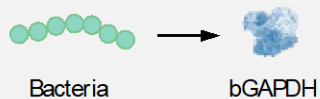
* Limited serotype protection (Pevnar - 13, Pneumovax - 23, Synflorix - 10)

** Also known as GBS (low incidence / high severity)

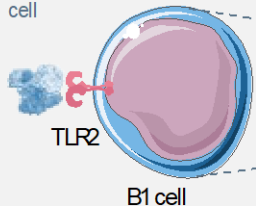
Bacteria use extracellular GAPDH to inhibit host immune response

Without PNV: Bacteria uses extracellular GAPDH to inhibit host Immune response

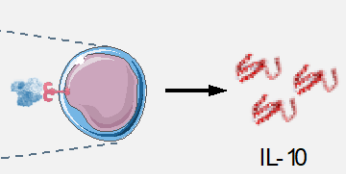
1 Bacteria excretes GAPDH



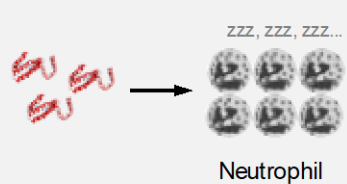
2 bGAPDH binds to TLR2 at B1 cell



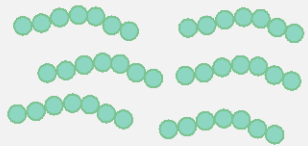
3 This leads to IL-10 production



4 Stops neutrophil recruitment

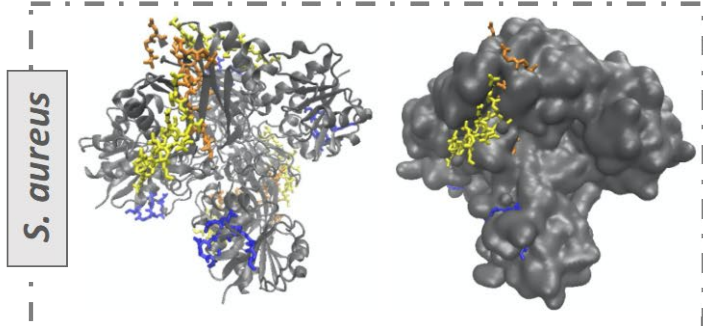
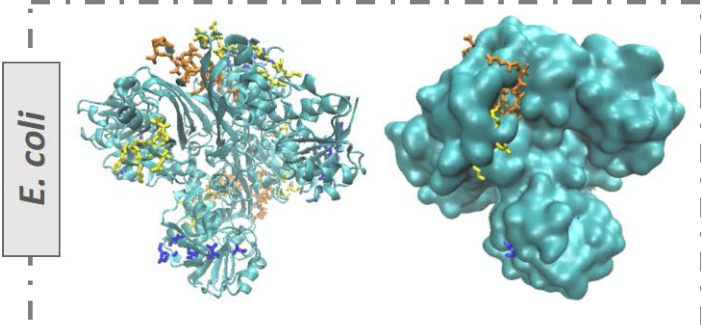
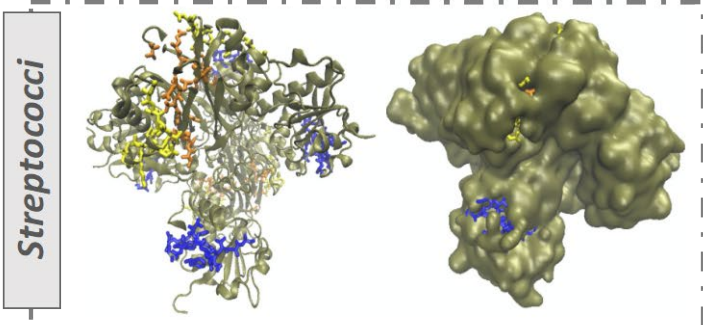


5 Uncontrolled Infection



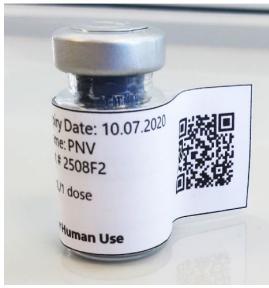
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Selection of peptides absent from human GAPDH



Criteria for peptide selection

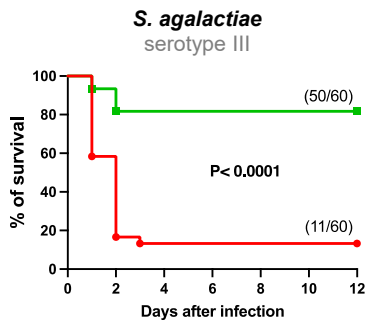
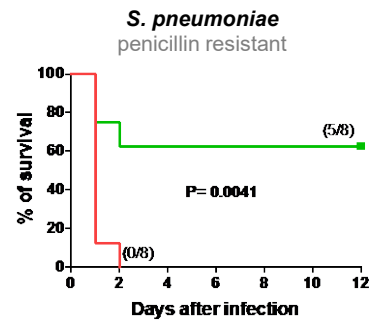
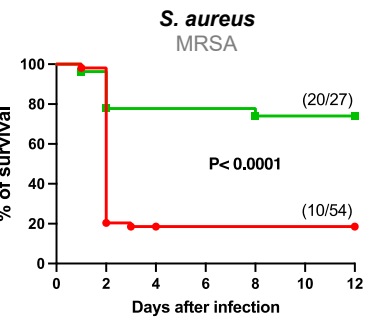
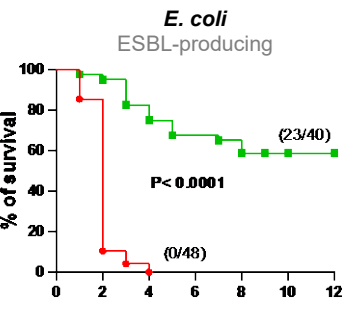
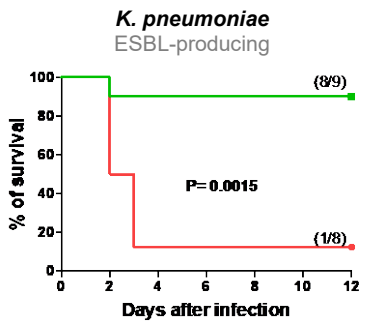
- Surface exposed bGAPDH peptides;
- Not present in human GAPDH;
- Peptide size from 8 to 20 amino-acids
- Conjugated to large carrier protein (KLH)



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PNV successfully concluded animal trials and is ready for Human Clinical Trials

Survival Rate with PNV (cPNV4)



K. pneumoniae
89% vs 13%

E. coli
58% vs 0%

S. aureus
73% vs 19%

S. pneumoniae
63% vs 0%

S. agalactiae
83% vs 18%

Vieira et al. Unpublished Data



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	Preclinical	Phase I	Phase II	Phase III	Market available	
		IMMUNETHERP - PNV				<p>\$5.9B PREVNAR revenue 2020</p> <p>\$1.6B PNEUMOVAX revenue 2020</p>
	<p><i>Streptococcus pneumoniae</i></p>			<p>NO Available Vaccines</p>		
	<p><i>Staphylococcus aureus</i></p>			<p>NO Available Vaccines</p>		
	<p><i>Klebsiella pneumoniae</i></p>			<p>NO Available Vaccines</p>		
	<p><i>Escherichia coli</i></p>				<p>NO Available Vaccines</p>	
<p><i>Streptococcus agalactiae</i></p>			<p>NO Available Vaccines</p>			

PNV has the potential to become the 1st vaccine in the world effective against all serotypes of these 5 deadly bacteria

* 20 serotypes
 ** 15 serotypes

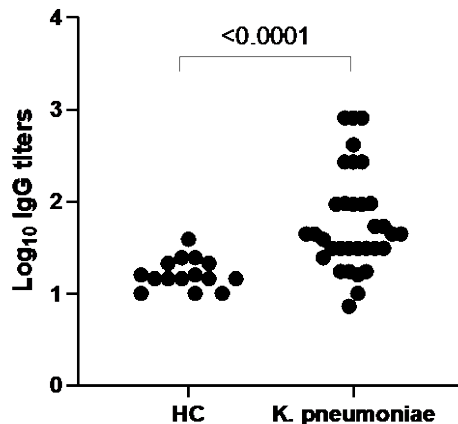
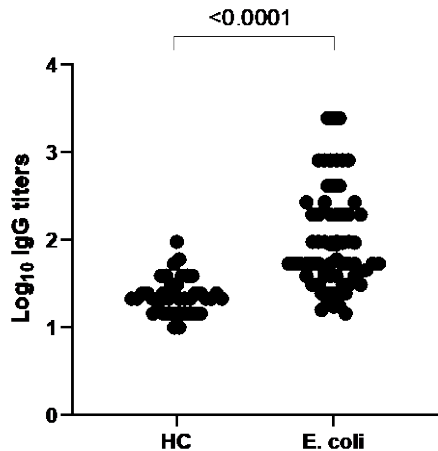


A close-up photograph of a hand with the index finger pointing towards the right, positioned on the left side of the slide. The background is a dark, textured surface.

*GAPDH as a target
Clinical Data*

Normalized Titers

Infected samples show high titers of IgG specific to bacterial surface
- Isopropanol-fixed bacteria or recombinant *S. aureus* *isdA* were used for ELISA plate coating



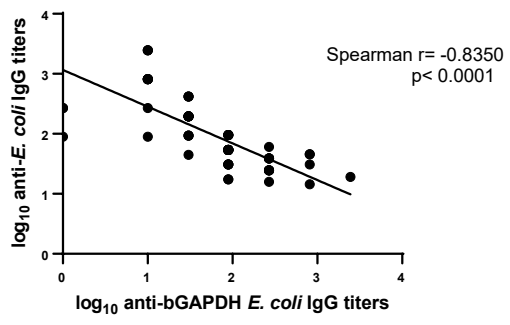
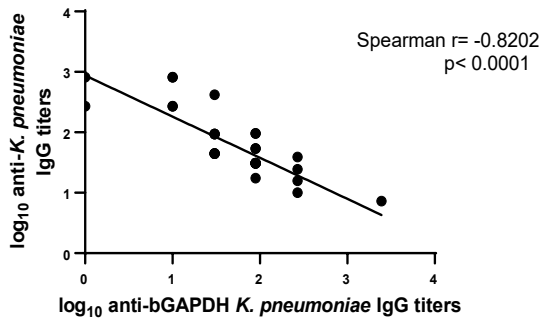
125 individuals with proven bacterial infection

- *E. coli*: 90 individuals
- *K. pneumoniae*: 35 individuals

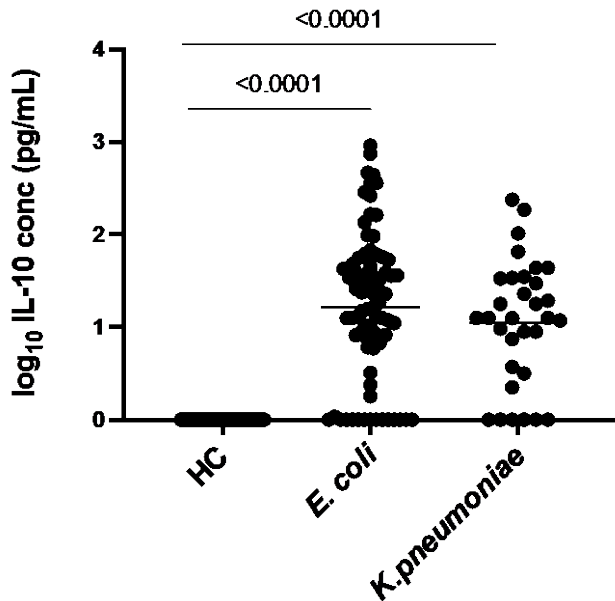
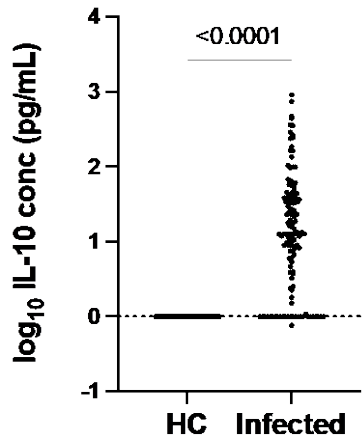
80 Healthy Controls (HC)

Normalized Titers

Infected samples show high titers of IgG specific to bacterial surface
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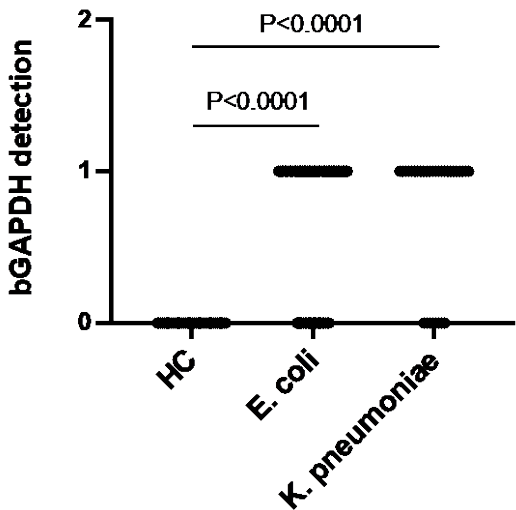


IL-10 concentration in infected patients



- Individuals with proven bacterial infection had significantly higher IL-10 concentration in the blood when compared with healthy controls.
- No IL-10 was detected in the blood of healthy controls.

Detection of bGAPDH in infected patients



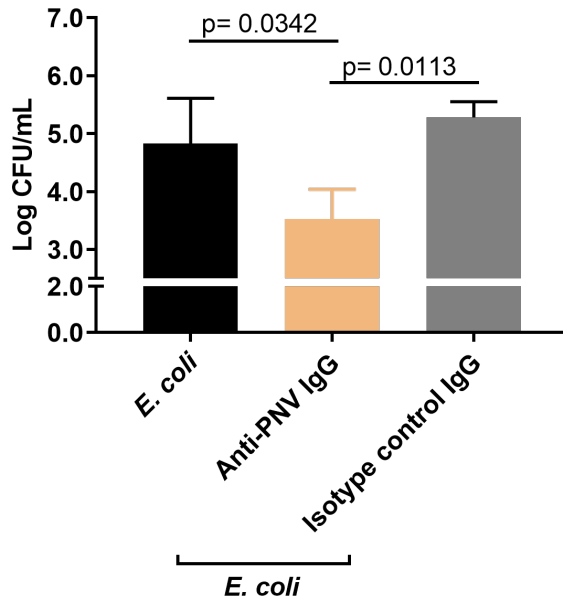
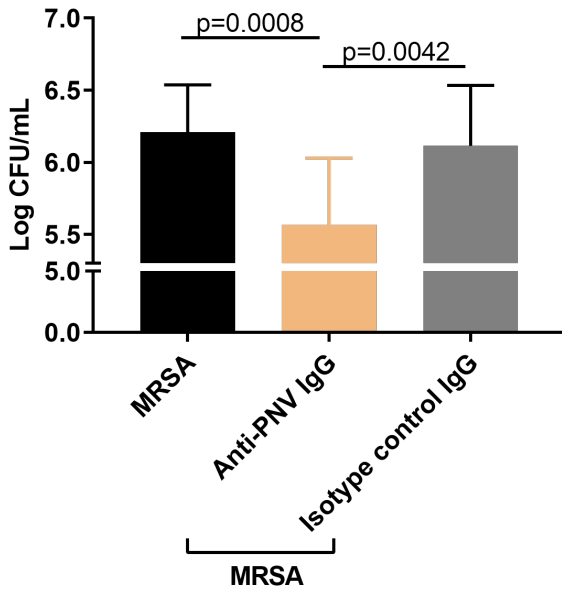
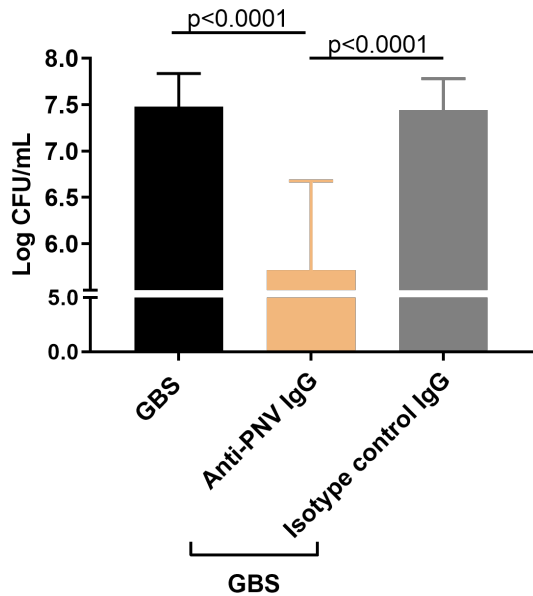
	% GAPDH*
HC	0
<i>E. coli</i>	69
<i>K. pneumoniae</i>	75

* Percentage of samples where GAPDH was detected

Bacterial GAPDH can be detected in the blood of 70% of the infected individuals

The presence of bacterial GAPDH in the plasma of infected patients and healthy controls was performed by ELISA and confirmed (double-checked) by Mass-Spec.

- All the plasma samples were centrifuged (10,000g) and filtered (0,2 μm) to exclude the presence of bacteria

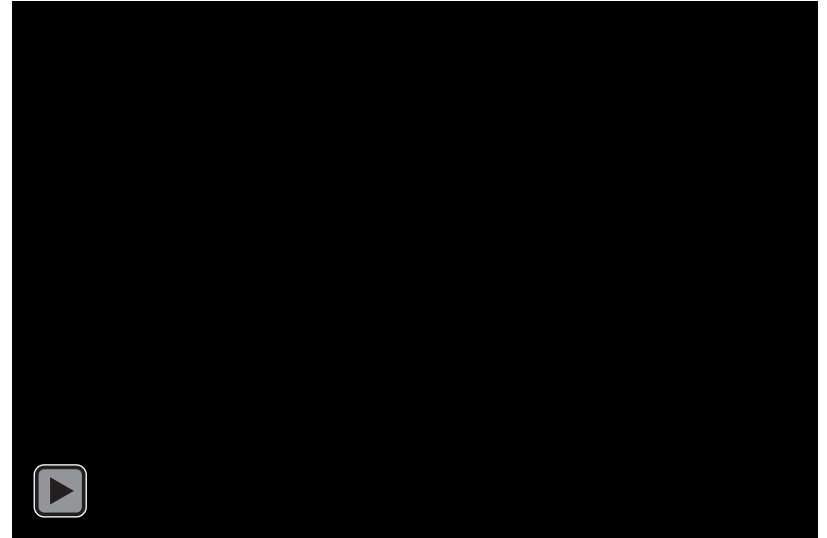
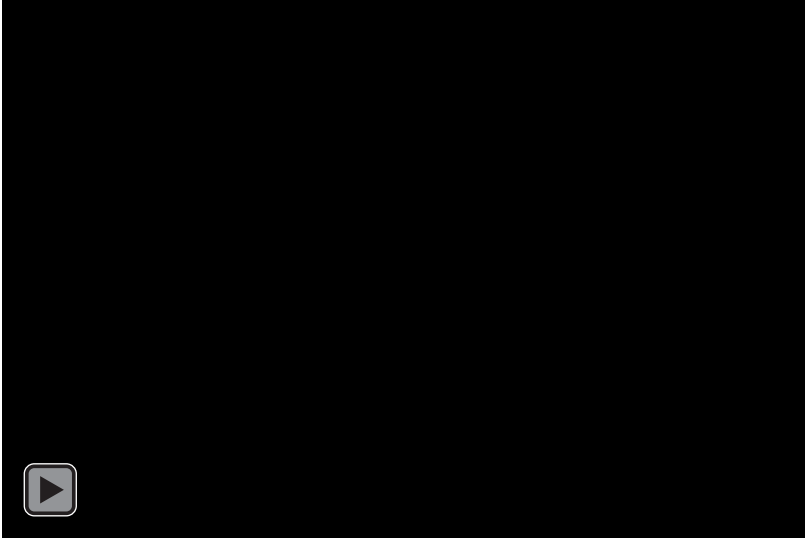


Purified anti-cPNV4 IgG reduces bacteremia in cord-blood

Total cord-blood cells were plated in 24-well plate (10^7 cells/well). *S. aureus*, *E. coli* or *S. agalactiae* cells were added at a multiplicity of infection (n° cord-blood cells/ n° bacteria cells) of 1 in the presence of 200 μ g of purified anti-cPNV4 IgG or anti-KLH IgG (isotype control). Cell cultures were incubated for 3h at 37°C with gentle shaking. At the end of the incubation period, bacterial CFU were quantified in the supernatants. Graphics represent data from at least 11 independent experiments with cells from 40 different donors. Cord-blood was obtained from Coimbra University Hospital upon informed consent.



Our Immune system has a unique ability to “sense danger”



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