



# Frontiers in Translational Medicine: The Clinician-Scientist Perspective

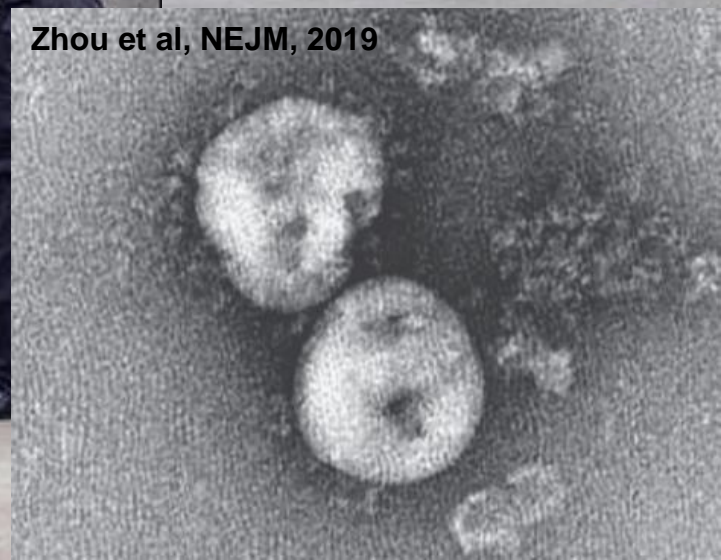
**Susanne Herold, MD, PhD**

Clinical Research Unit *Virus-induced Lung Injury*  
& Clinical Infectious Diseases  
Universities of Giessen & Marburg Lung Center  
Department of Medicine II  
German Center for Lung Research (DZL)





Zhou et al, NEJM, 2019





# Frontiers in Translational Medicine: From infection research to new antiviral drugs

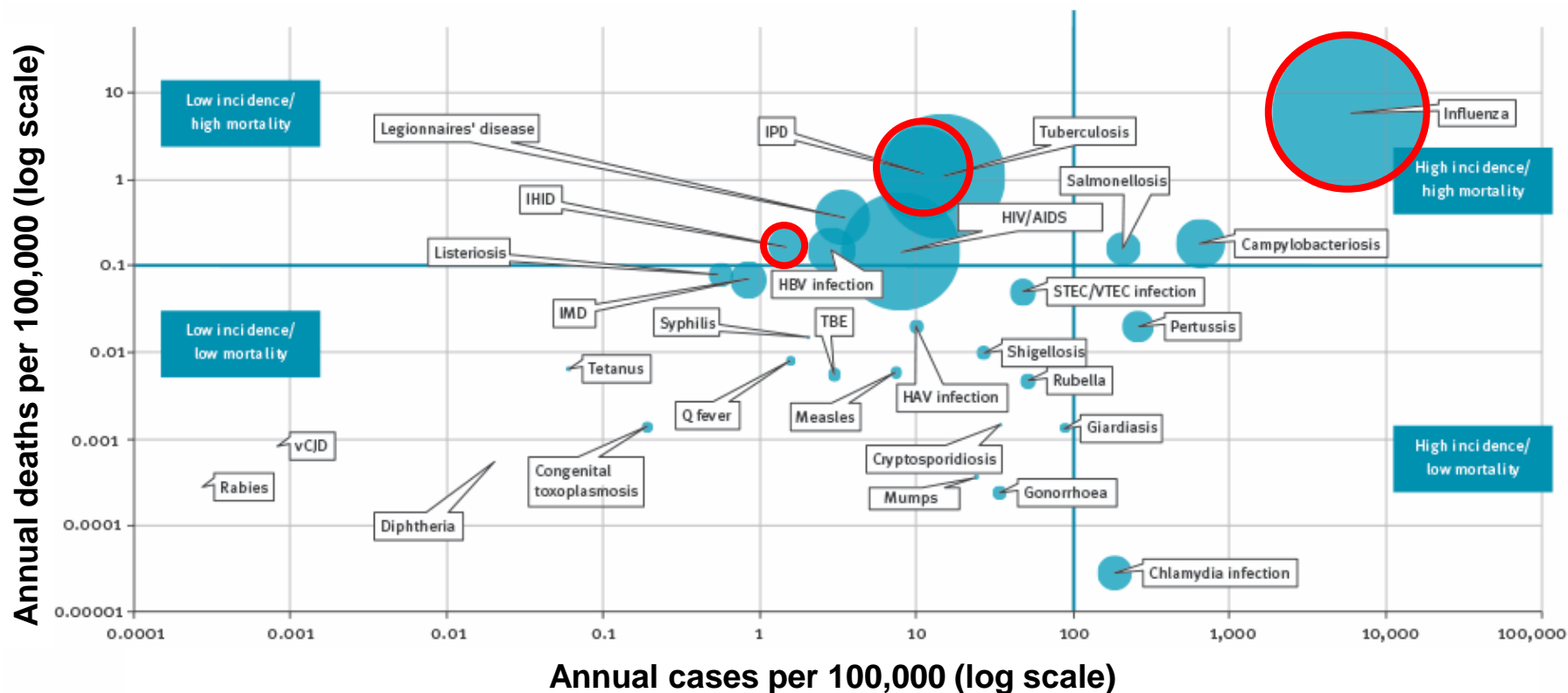
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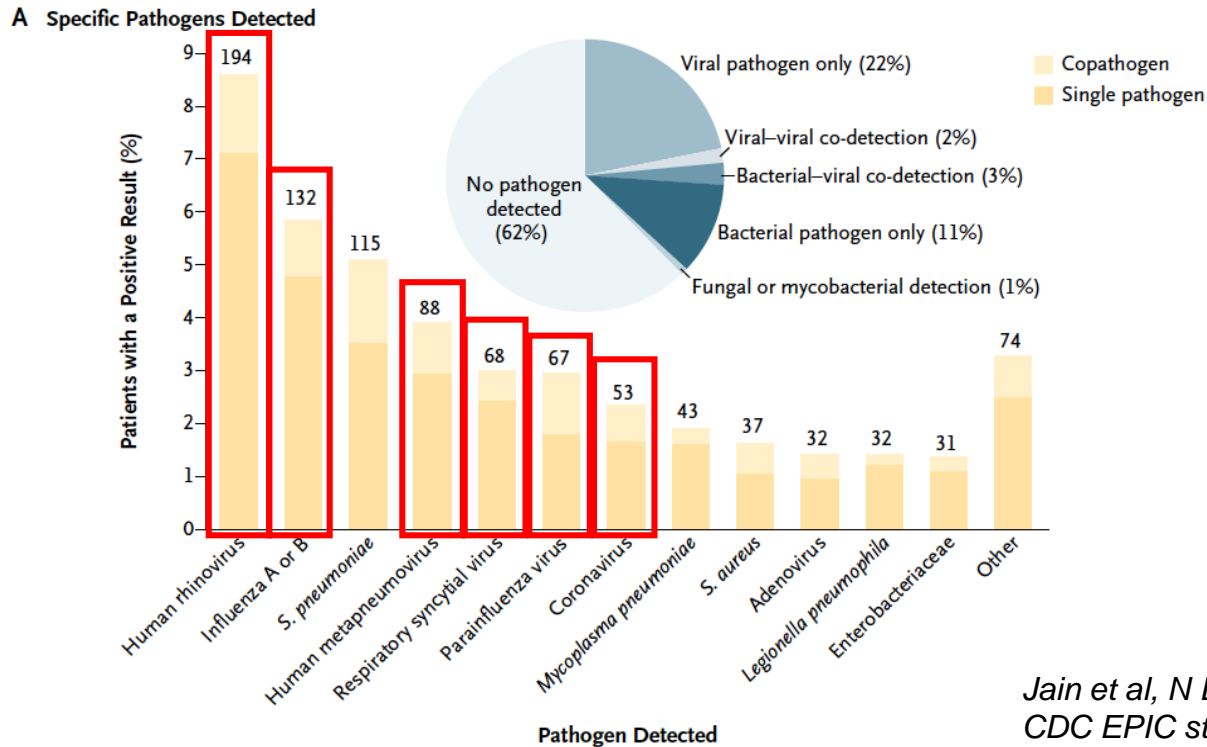
# Importance of the research topic: High disease burden

EU countries 2009-13:



Bubble diameter: number of *Disability-adjusted life years (DALYs)* per 100,000 population per year.

# Importance of the research topic: High disease burden



- **Respiratory viruses** account for a large number of **severe pneumonia** cases worldwide
- **Increased susceptibility** of patients with **chronic lung diseases**, that are typically triggered and exacerbated by viral infections (IPF, COPD/Asthma, BPD)
- **Emerging** respiratory viruses like **2019-nCoV**, SARS- or MERS-CoV and HPAIV with **high pathogenicity and pandemic potential**

# Importance of the research topic: High medical need

In striking  
contrast.....

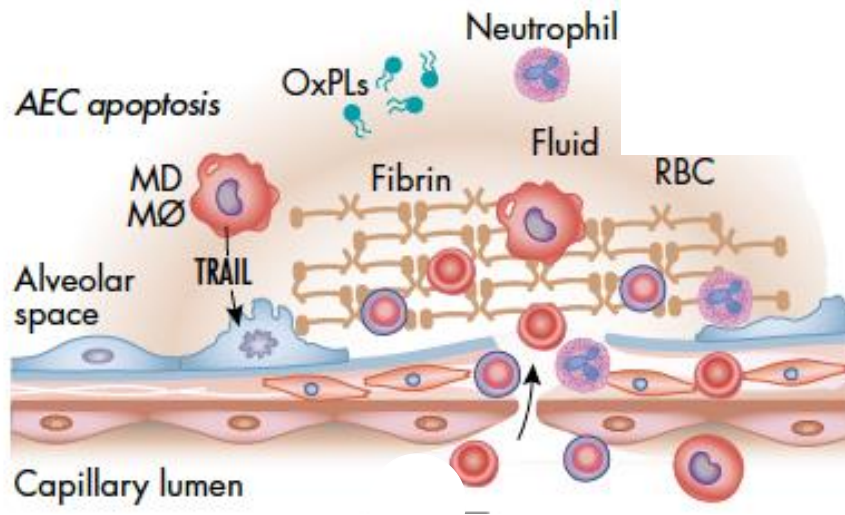


51 years, male, influenza H1N1, UKGM, 2010

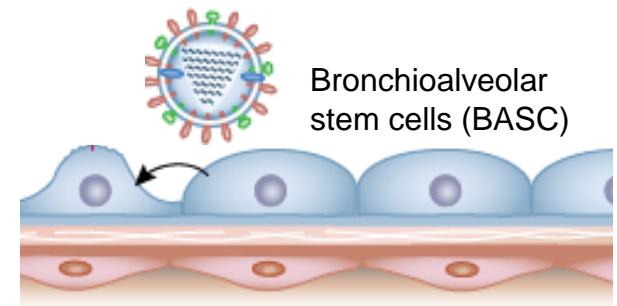
- Few **antivirals** with **limited efficacy** (only influenza)
- **No causal treatment** for Acute Respiratory Distress Syndrome (ARDS)
- Influenza **vaccine with limited protection**, no vaccine against all other respiratory viruses available

# Distal lung virus infections result in severe damage of the alveolar epithelium

**AEC injury by exaggerated/  
unbalanced host responses**



**Resolution and  
epithelial repair**



Herold & Sander, *Science*, in press  
Peteranderl et al, *J Clin Invest*, 2016  
Högner et al, *PLoS Pathog*, 2013  
Unkel et al, *J Clin Invest*, 2012  
Herold et al, *J Exp Med*, 2008

Salwig et al, *EMBO J*, 2019  
Quantius et al, *PLoS Pathog*, 2016  
Herold et al, *Am J Respir Crit Care Med*, 2014  
Herold et al, *Am J Respir Crit Care Med*, 2011  
Cakarova et al, *Am J Respir Crit Care Med*, 2009

Herold et al, *Eur Resp J*, 2015

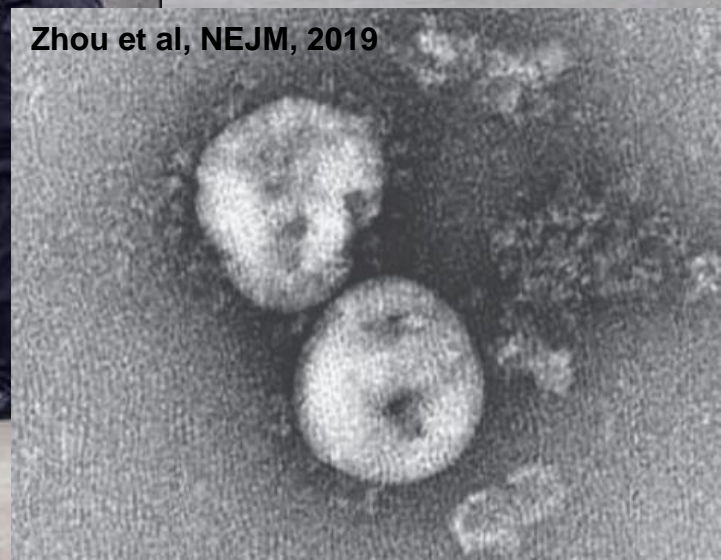
# Overall strategic aims

1. Gain better understanding of the molecular interactions at the ***virus-host interface*** to design effective ***antivirals*** (with broad antiviral capacity)
2. To elucidate how viral infection
  - ***drives both structural and functional damage*** to different cellular compartments of the distal lung
  - impacts ***mechanisms of injury resolution and lung regeneration*** in immunocompetent hosts and patients with pre-existent chronic lung diseases
3. To ***integrate and translate these findings into novel treatment strategies*** including host-based interventions towards first-in-human studies.

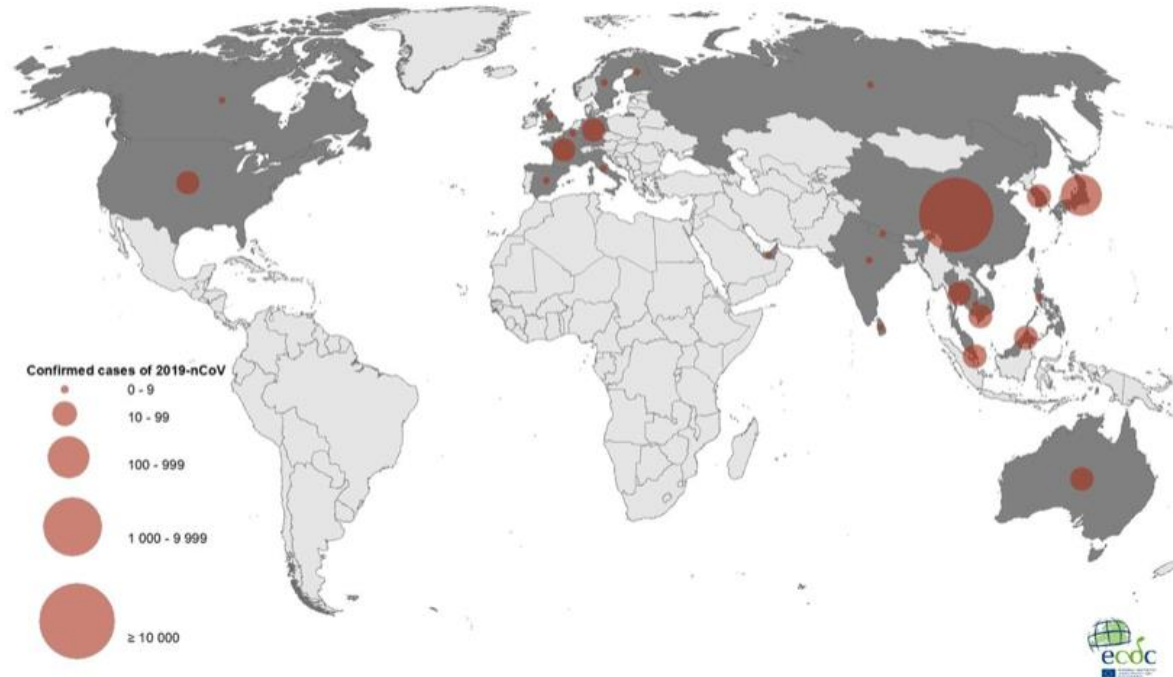




Zhou et al, NEJM, 2019



# 2019-nCoV (SARS-CoV-2)



Jan 23, 2020:

## Pneumonia cases associated with novel coronavirus, China

**448 lab-confirmed cases** of novel coronavirus

**9 deaths** in Wuhan, China

**Thailand, Japan, South Korea, USA** report imported cases



Feb 11, 2020:

**43 118 lab-confirmed cases** of novel coronavirus

**1018 deaths** one outside China (Philippines)

**41 cases** reported in the EU/EEA and the UK

# Covid-19 FACTS

- Accumulation of pneumonia cases in Dec 2019 in Wuhan
- Experts from the CCDC arrive in Wuhan on Dec 30th and inform WHO
- Primary infection probably at a local animal market; no human-to-human transmission
  
- 7th January 2020: official announcement of the appearance of a novel Coronavirus of the family of betacoronaviridae, approved by WHO on 9th Jan 2020
  
- 13th Jan 2020: genome sequence available on NCBI
- 16th Jan 2020: diagnostic test released
  
- 88% sequence identity to bat SARS-like CoV (79% to SARS-CoV) *Lu et al, Lancet 2020*; same receptor for cell entry (ACE-2)
  
- Human-to-human transmission soon confirmed; detection of virus particles in mucous membranes, blood and stool of infected patients; droplet transmission, faecal-oral (?)
- Incubation period 2-14 (21?) days
- Asymptomatic to severe pneumonia; fever, cough, sore throat; fatality rate 2% (?)

To date, there is no specific medicine recommended to prevent or treat the new coronavirus (2019-nCoV).

However, those infected with the virus should receive appropriate care to relieve and treat symptoms, and those with severe illness should receive optimized **supportive care.**

Some specific treatments are under investigation, and will be tested through clinical trials.

WHO is helping to accelerate research and development efforts with a range of partners.



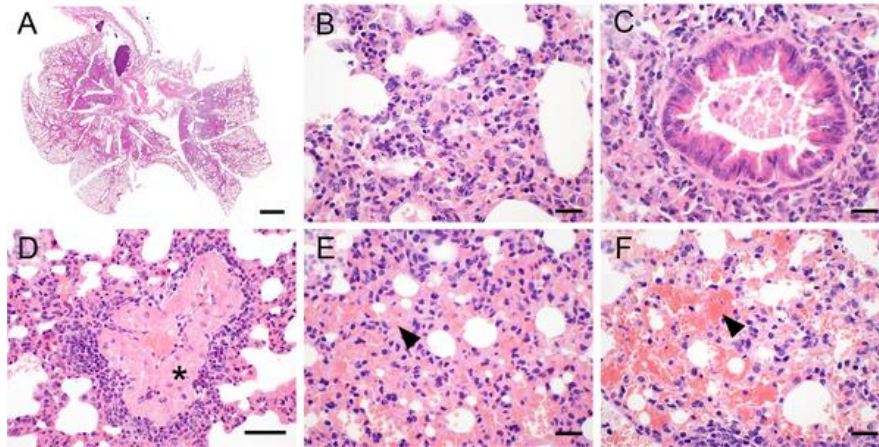
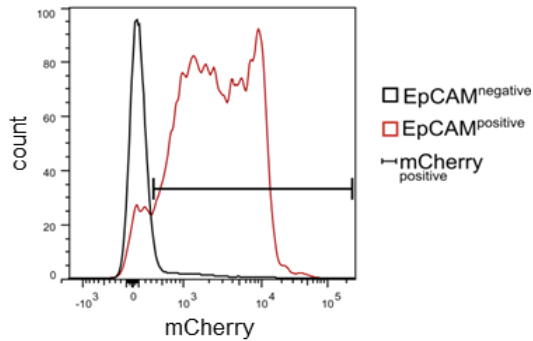
**#Coronavirus**

# Are there any specific medicines to prevent or treat the new coronavirus?

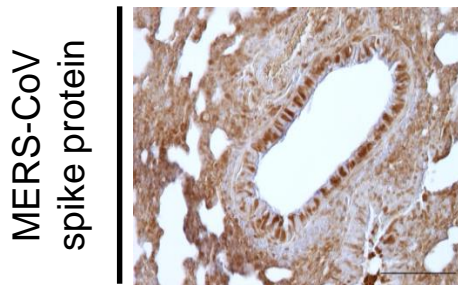
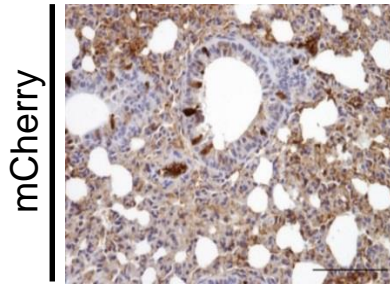


# Preclinical disease modeling: Developing a MERS-CoV in vivo model

Adenoviral transduction of hDPP4-mCherry by intratracheal application followed by intranasal MERS-CoV infection



Dietert et al., *PLoS ONE*, 2017



- necrotizing, bronchointerstitial pneumonia
- alveolar edema
- hemorrhage

Volz et al., *J Virol*, 2015

# Ongoing: Formulations for aerosolized deposition/compound modifications



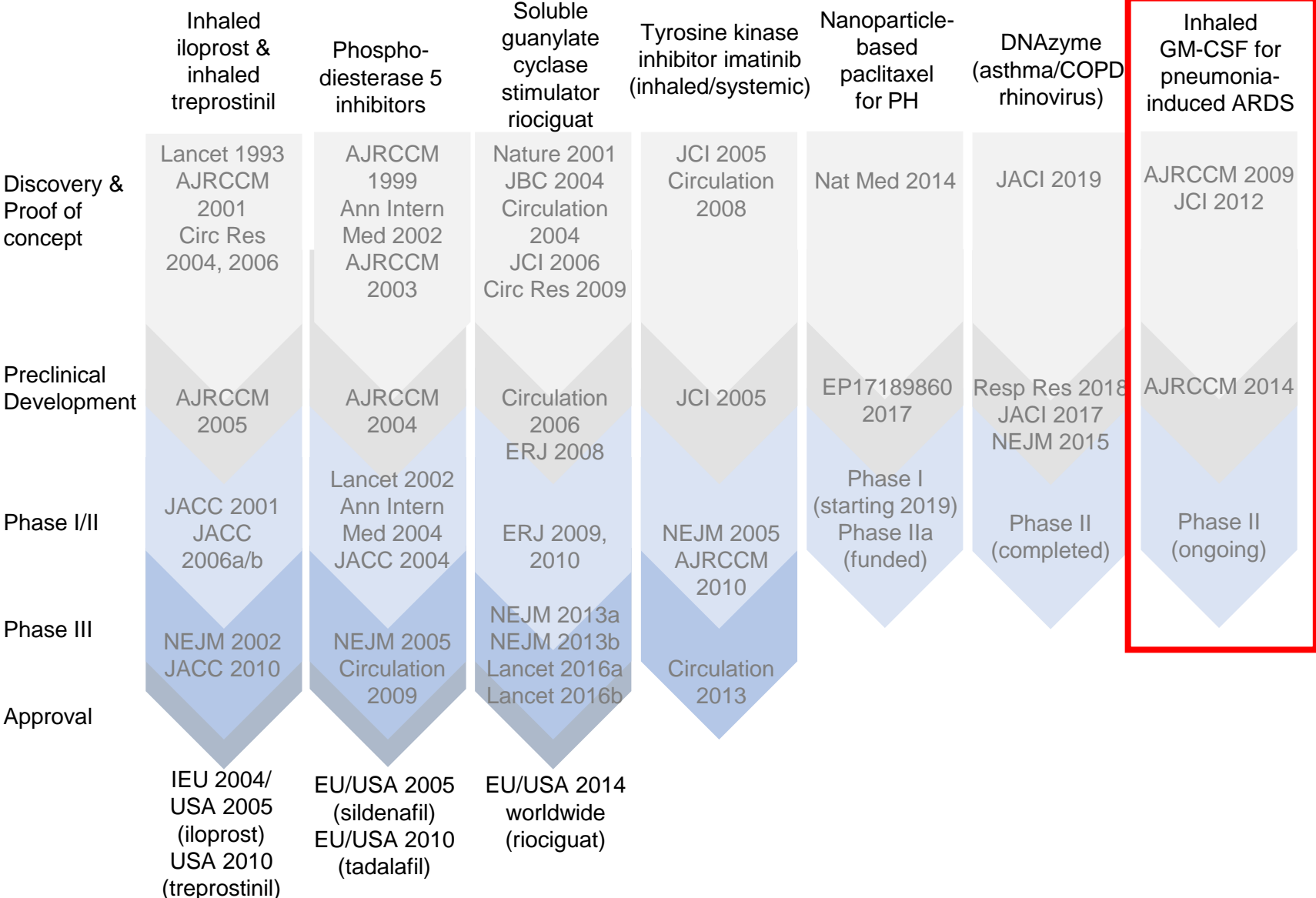
Partner Site BREATH  
Hannover



Fraunhofer-Institut für Toxikologie und  
Experimentelle Medizin

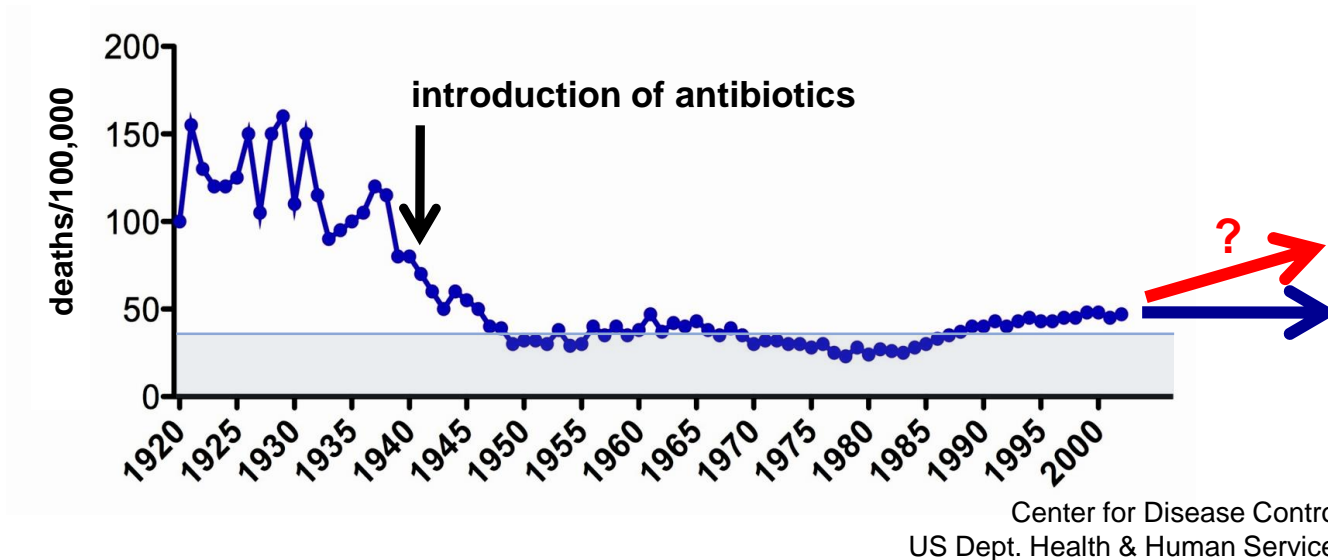
- Compound modifications
- Aerosolized deposition
- (Inhalation) toxicology
- .....
- First-in-man

# Successful translational pipeline for lung therapeutics established at the UGMLC



# Beyond viral pneumonia: sCAP and sCAP-associated Acute Respiratory Distress Syndrome

....the unmet medical need for adjunctive therapies



„Resistance to common bacteria has reached alarming levels in many parts of the world and in some settings, few, if any, of the available treatments options remain effective for common infections.“

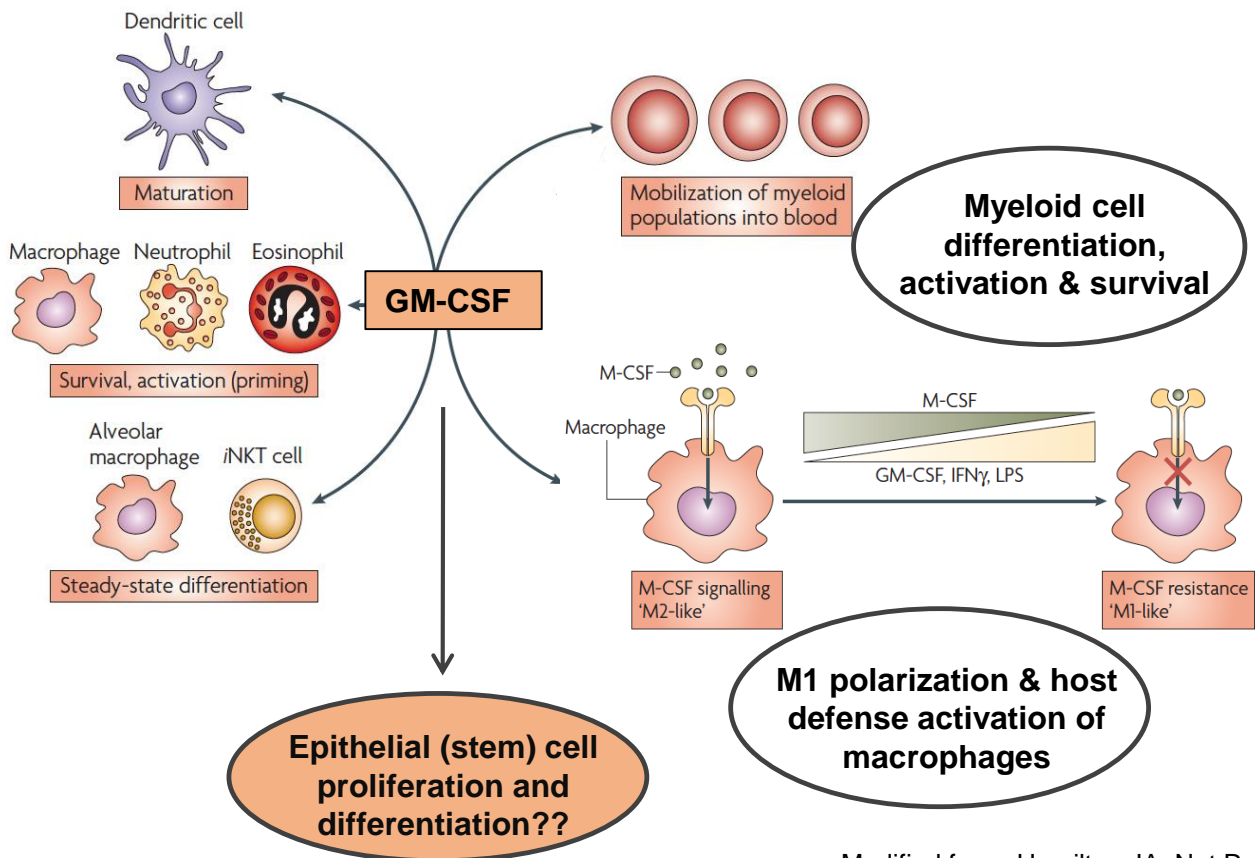
WHO, 2014



# Granulocyte/macrophage-colony stimulating factor



Lidija Cakarova,  
PhD student  
2006-09



Modified from Hamilton JA, Nat Rev Immunol, 2008

Am J Respir Crit Care Med, 2009

## Macrophage Tumor Necrosis Factor- $\alpha$ Induces Epithelial Expression of Granulocyte-Macrophage Colony-stimulating Factor Impact on Alveolar Epithelial Repair

Lidija Cakarova<sup>1</sup>, Leigh M. Marsh<sup>1</sup>, Jochen Wilhelm<sup>2</sup>, Konstantin Mayer<sup>1</sup>, Friedrich Grimminger<sup>1</sup>, Werner Seeger<sup>1</sup>, Juergen Lohmeyer<sup>1</sup>, and Susanne Herold<sup>1</sup>

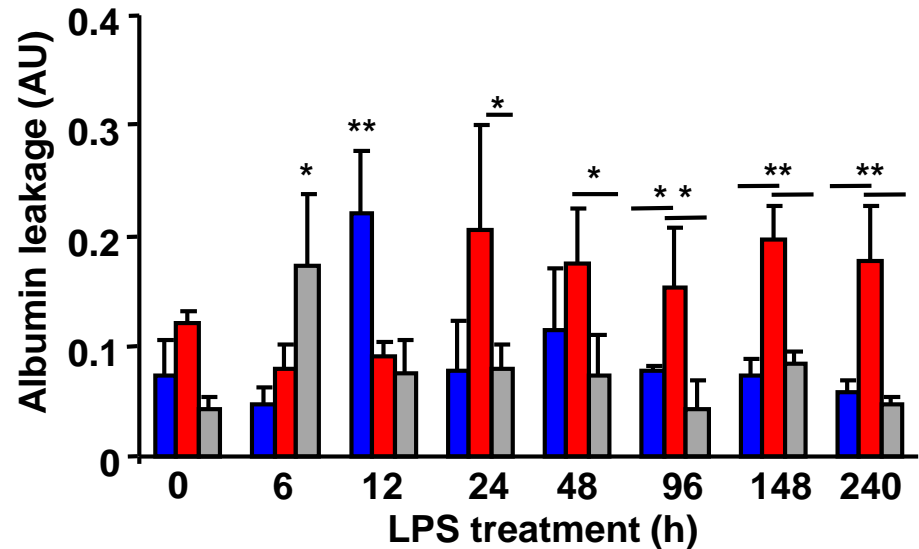
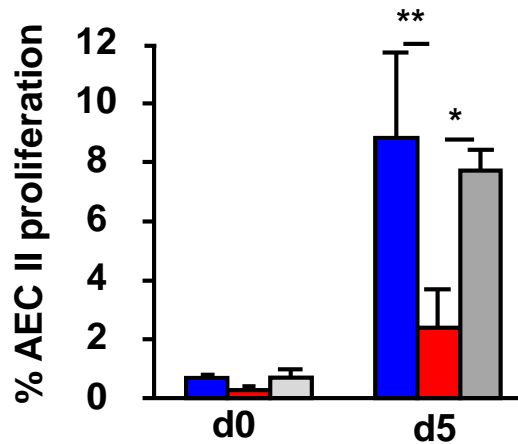
# GM-CSF mediates lung (alveolar) epithelial cell proliferation and restoration of lung barrier function



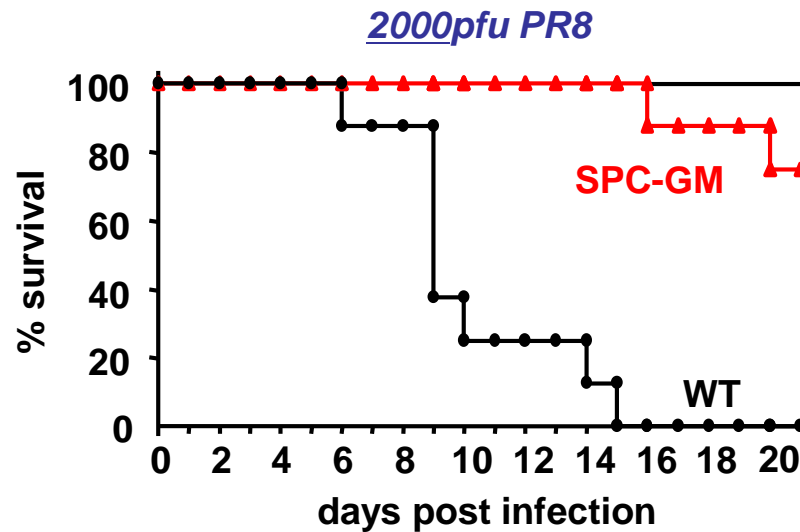
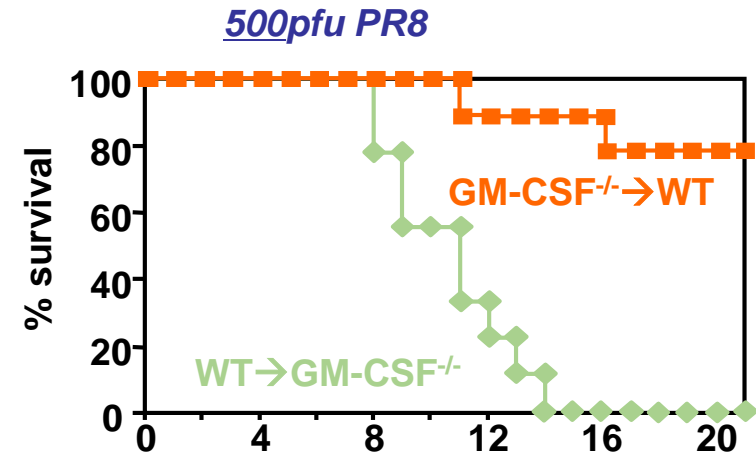
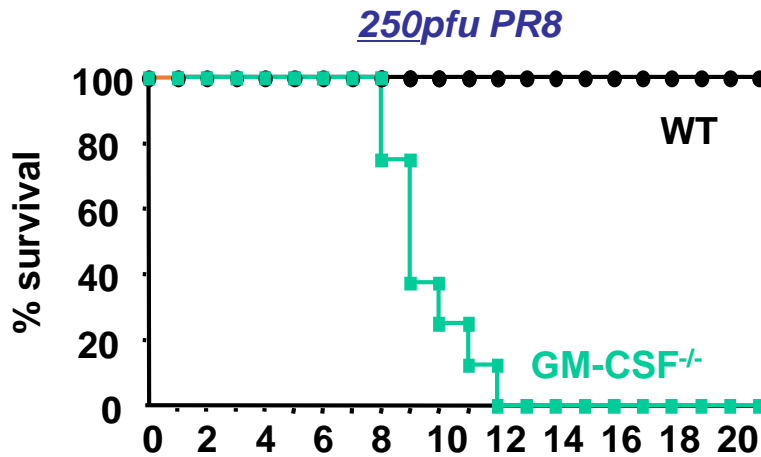
LPS 50 $\mu$ g /  
2.5x10<sup>4</sup> *K.pn.* it

- wt
- GM-CSF<sup>-/-</sup>
- SPC-GM

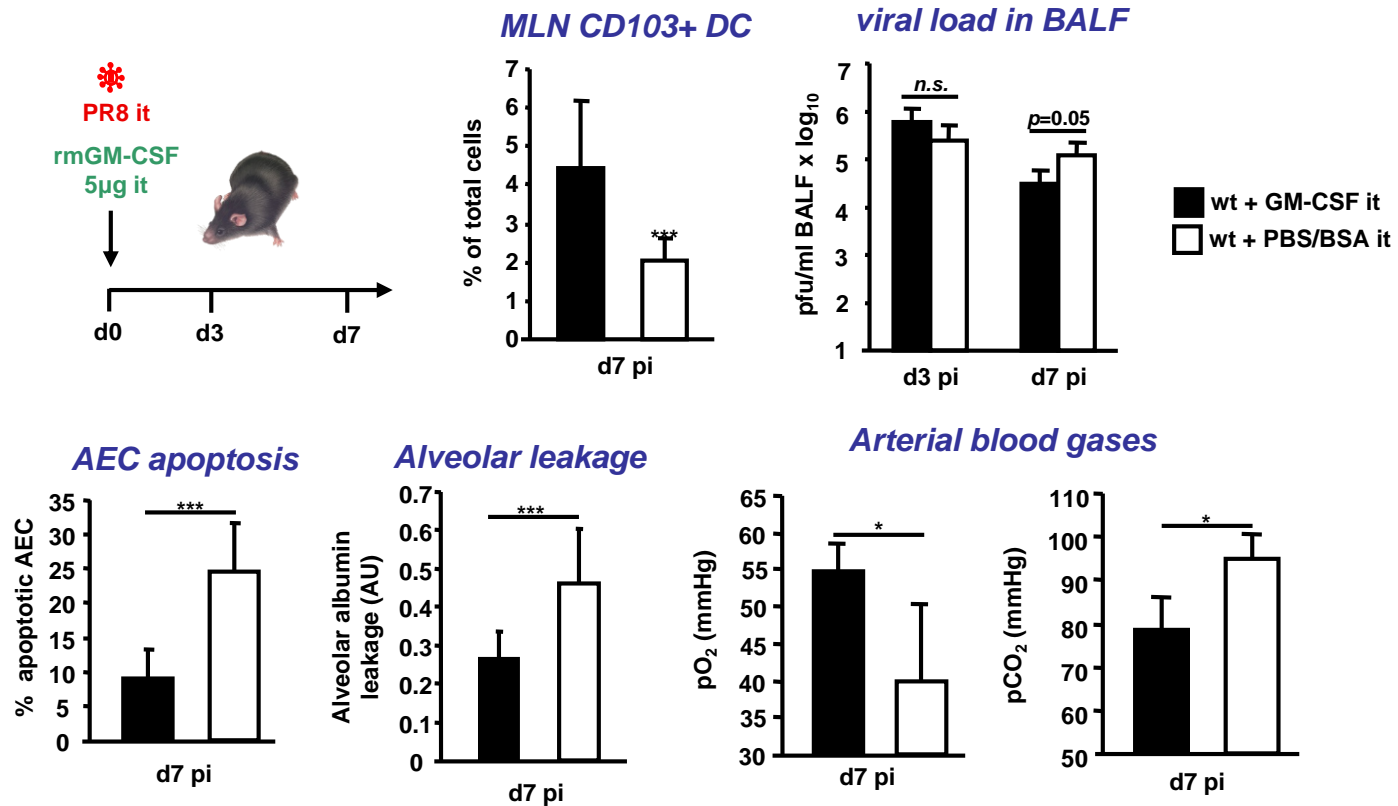
GM-CSF<sup>-/-</sup> with constitutive alveolar overexpression of GM-CSF



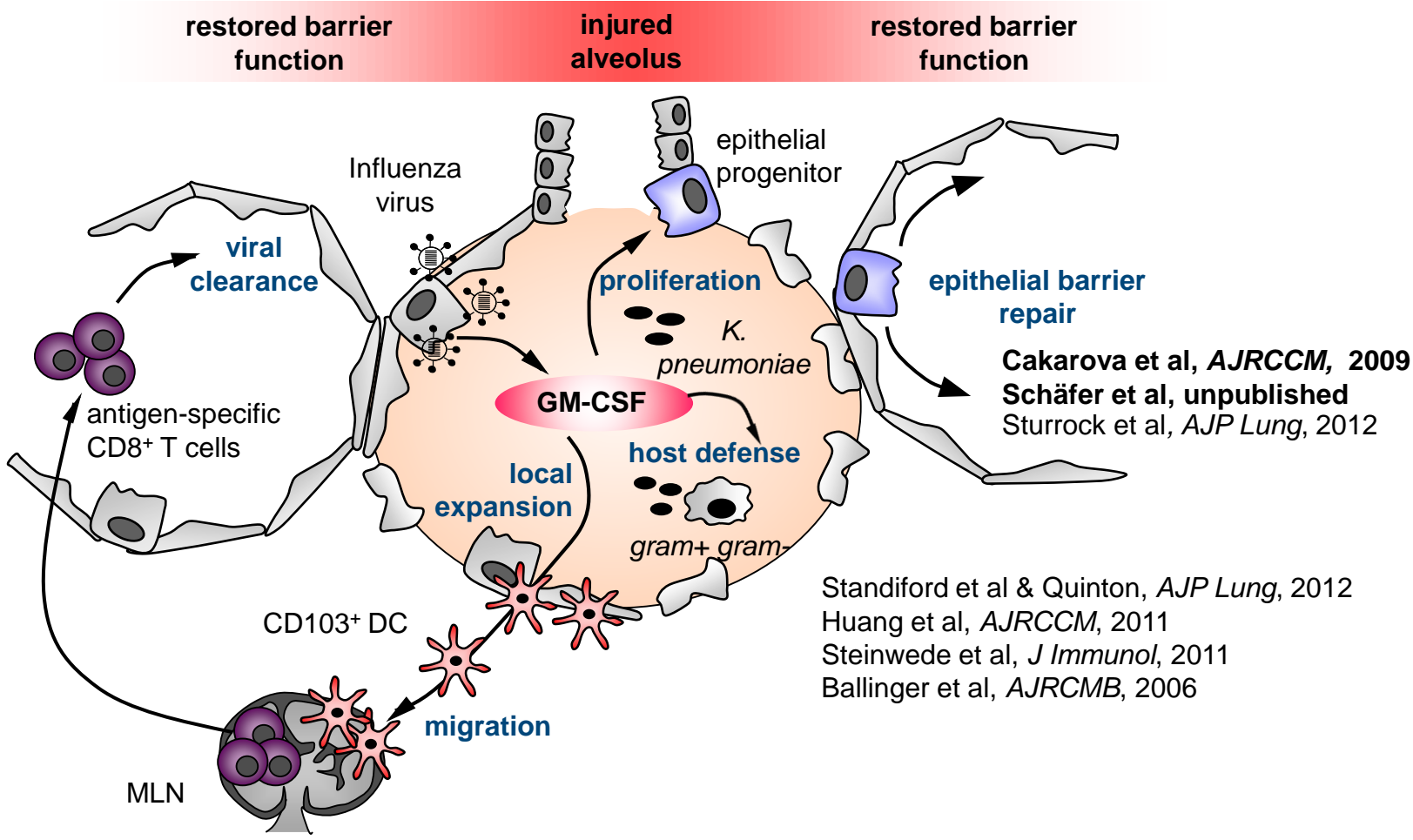
# AEC II expressed GM-CSF increases survival after influenza virus (IV) infection



# Intratracheal GM-CSF application reduces lung injury during influenza virus infection



# Summary of findings on GM-CSF effects in pre-clinical animal models



Cakarova et al, *AJRCCM*, 2009  
 Schäfer et al, unpublished  
 Sturrock et al, *AJP Lung*, 2012

Standiford et al & Quinton, *AJP Lung*, 2012  
 Huang et al, *AJRCCM*, 2011  
 Steinwede et al, *J Immunol*, 2011  
 Ballinger et al, *AJRCMB*, 2006

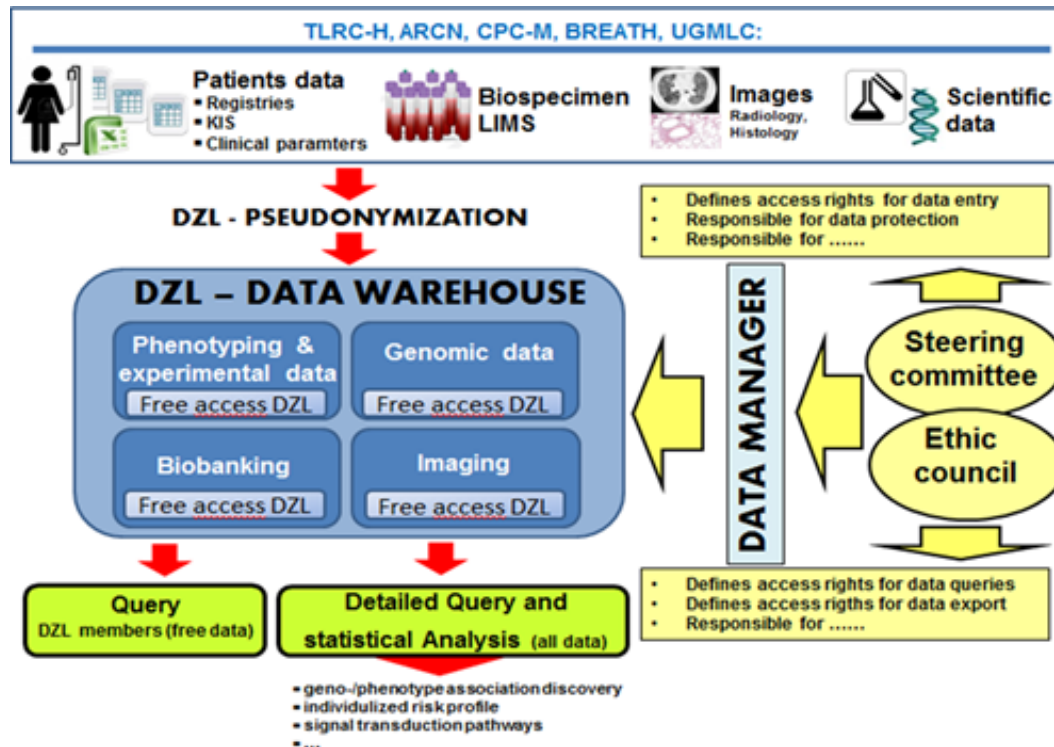
Unkel et al, *J Clin Invest*, 2012

# GM-CSF inhalation as compassionate treatment in severe CAP-associated ARDS

## → Bedside-to-Bench



Deutsches Zentrum für  
Lungenforschung

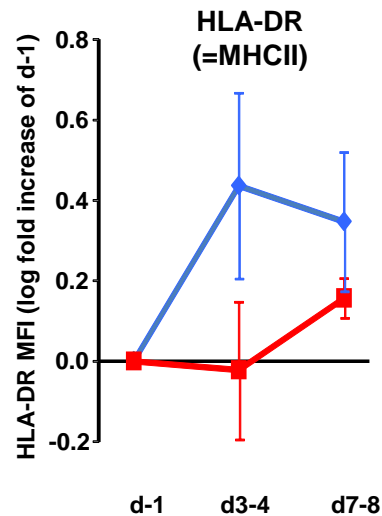
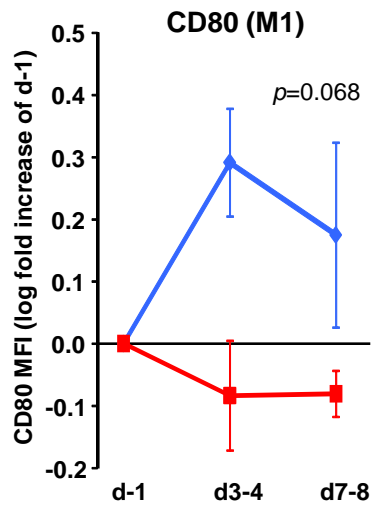


Phenotype Disease-Area (# patients) – DZL Biobank	Feb 19
Asthma and Allergy (AA)	1610
Benign lesions	506
Bronchopulmonary Dysplasia (BPD)	141
Cancer	4687
COPD	4059
Cystic Fibrosis (CF)	374
Diffuse parenchymal lung dis. (DPLD)	3340
End stage lung disease (ESLD)	322
Healthy Controls	152
<b>Pneumonia/ARDS</b>	<b>12431</b>
Pulmonary Hypertension (PH)	1703
Tuberculosis (TB)	164

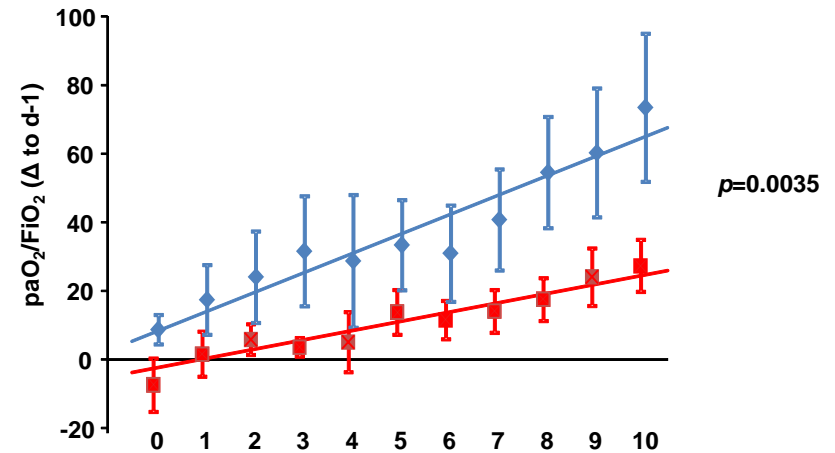
# GM-CSF inhalation activates macrophages and improves oxygenation in CAP-associated ARDS (n=6)

—◆— GM-CSF  
—■— untreated

### pulmonary macrophage activation



### oxygenation



→ Reduction in morbidity scores (SAPS,  $p=0.036$  and SOFA,  $p=0.068$ )

# Lost in translation? Death valley No 1...



## SERENDEX

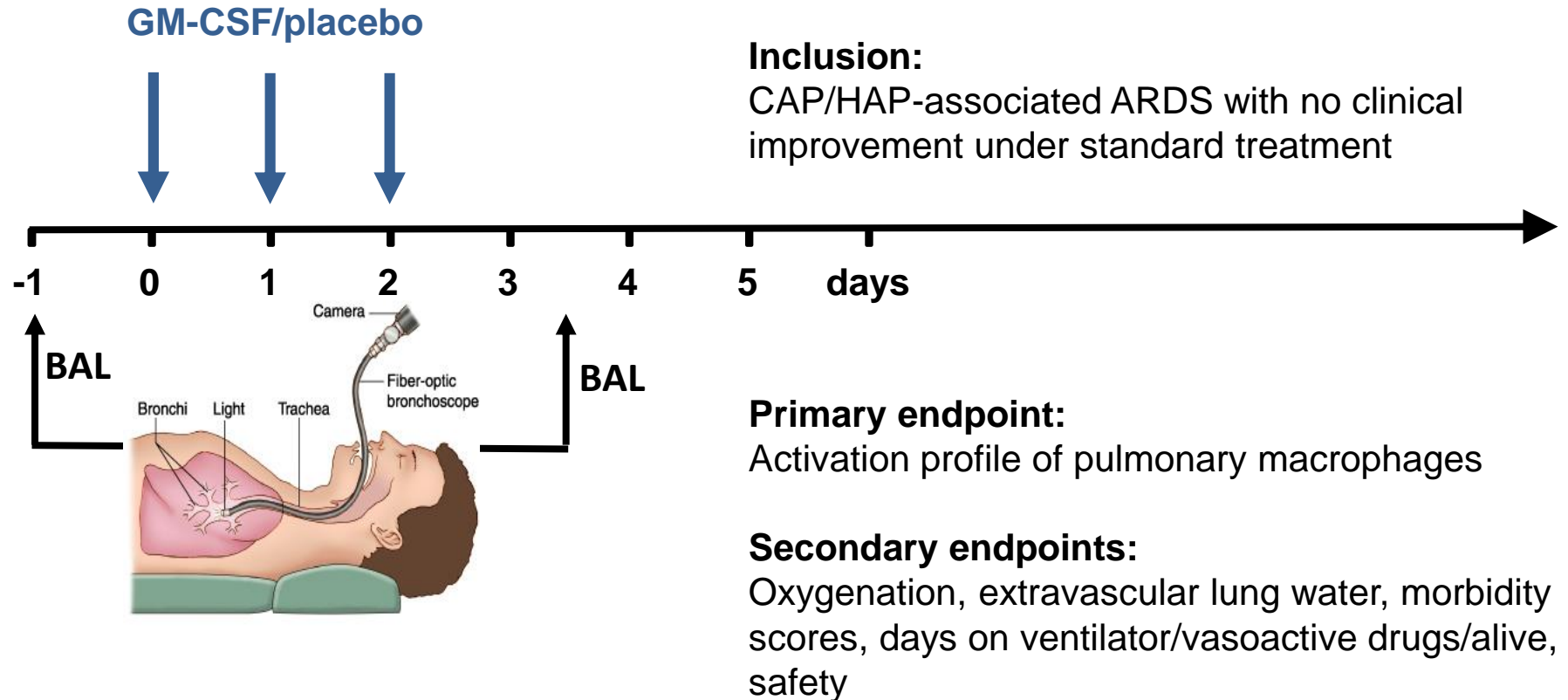
### INHALATION OF GM-CSF IN ARDS – INVESTIGATOR MEETING

- Preclinical testing of inhaled GM-CSF in cynomolgous macaques done
- Phase I healthy volunteers running



# GI-HOPE (Gm-csf Inhalation to improve HOst defense and Pulmonary barrier rEstoration)

A randomized, double-blind, placebo-controlled, multicenter Phase II trial



**SERENDEX**  
Pharmaceuticals

GREAT BEGINNINGS WITH  
GIESSEN



...but a rapid ending



**SAVARA**



withdrawal of support of ARDS program upon stock  
market launch



Deutsches Zentrum für  
**Lungenforschung**

- Clinical trials program, 3 DZL sites, 3 non-DZL sites
- Recruiting patients
- Funding of an additional bedside-to-bench research program on single cell RNA-Seq phenotyping of BAL macrophages

# **Summary: Key elements and infrastructure relevant to enforce translation**

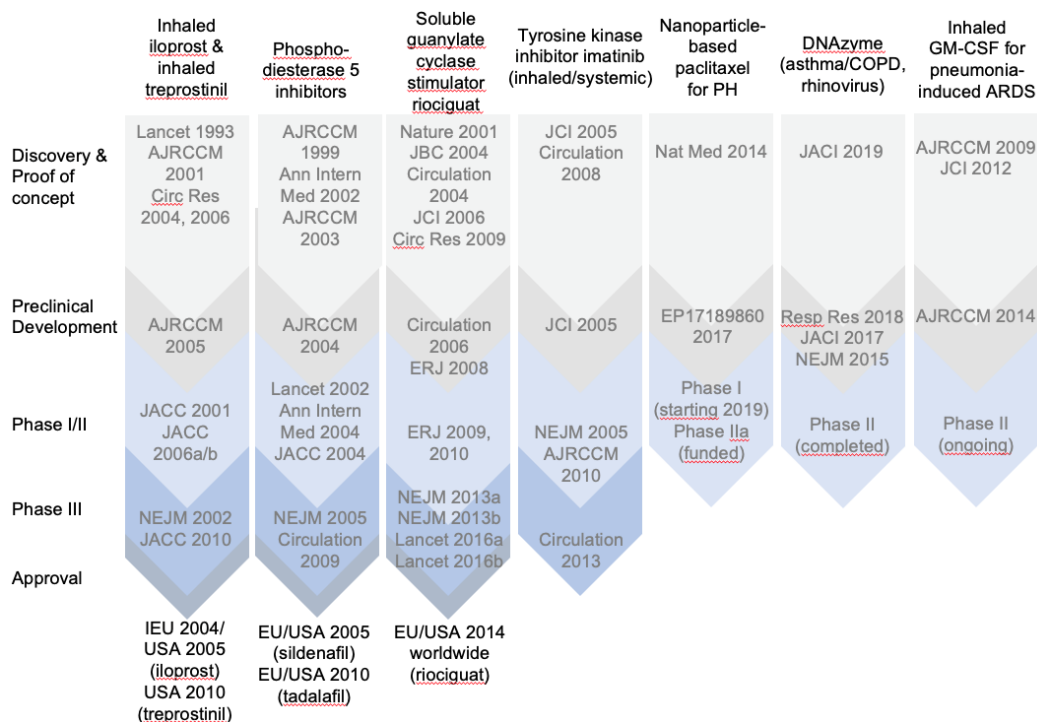
# Summary: Key elements and infrastructure relevant to enforce translation

- „**Basic biomedical research** to drive the discovery engine“ (*Duda GN et al, Sci Transl Med, 2014*) with relevant preclinical lung/infectious disease models in place



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- „**Basic biomedical research** to drive the discovery engine“ (*Duda GN et al, Sci Transl Med, 2014*) with relevant preclinical lung/infectious disease models in place
- **Repurposing** approach: Phase I rapidly accomplished for new application route (inhalation), collaborations with DZL-affiliated institutions (ITEM)
- **The mindset for translation:**
  - **Translational pipeline** and a local culture of building PPPs successfully established for PH, „**failure**“ accepted



# Summary: Key elements and infrastructure relevant to enforce translation

- „**Basic biomedical research** to drive the discovery engine“ (*Duda GN et al, Sci Transl Med, 2014*) with relevant preclinical lung/infectious disease models in place
- **Repurposing** approach: Phase I rapidly accomplished for new application route (inhalation), collaborations with **DZL**-affiliated institutions (ITEM)
- **The mindset for translation:**
  - **Translational pipeline** and a local culture of building PPPs successfully established for PH, „**failure**“ accepted
  - JLU **TransMIT** as hub for patenting and technology transfer issues in the value creation chain
  - **Clinician-Scientist programs** in place (DFG, CPI, **DZL**)
- **DZL Biobanking and Data Warehouse:** Bedside-to-bench approach allows for precision phenotyping and molecular characterization and therefore for better protocol design, and readout definition
  - ARDS: more a collection of different heterogenous syndromes than a disease definition – „**ARDS is the graveyard of pharmaceutical industry**“
- **DZL Clinical Trials** Infrastructure:
  - Clinical trial **funding** rapidly available after withdrawal of support by Savara
  - **KKS** (Study design, protocol submission, trial management)

# Finally: The Clinician-Scientist Perspective



A high-wire act between lab and clinics

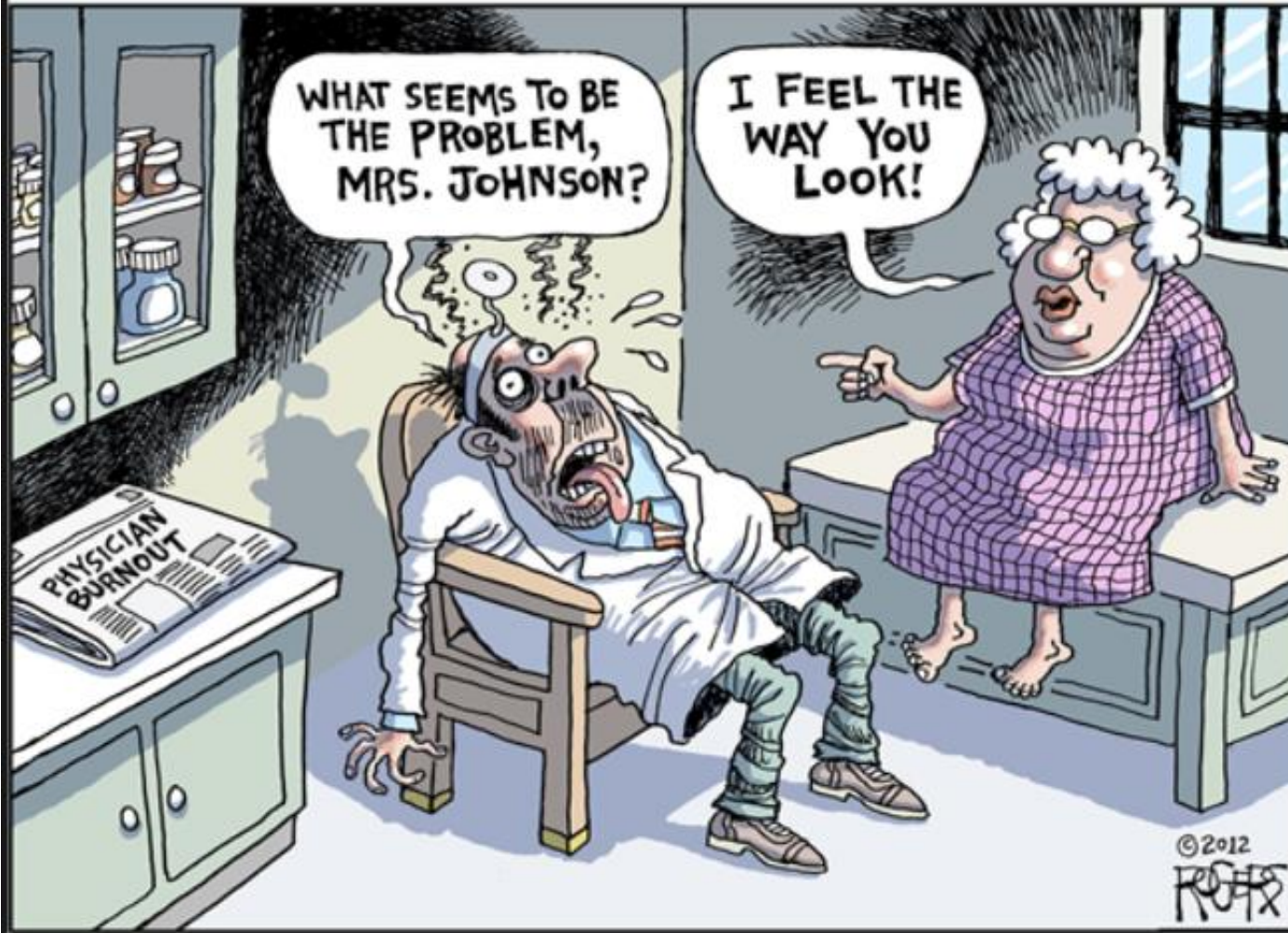


..... **trying to be good at both laboratory research and managing sick patients, one ends up by failing to do either well so that basic scientists are skeptical about your scientific knowledge and ability while your clinical colleagues do not regard you as a top-notch clinician**

# Finally: The Clinician-Scientist Perspective

SECOND OPINION

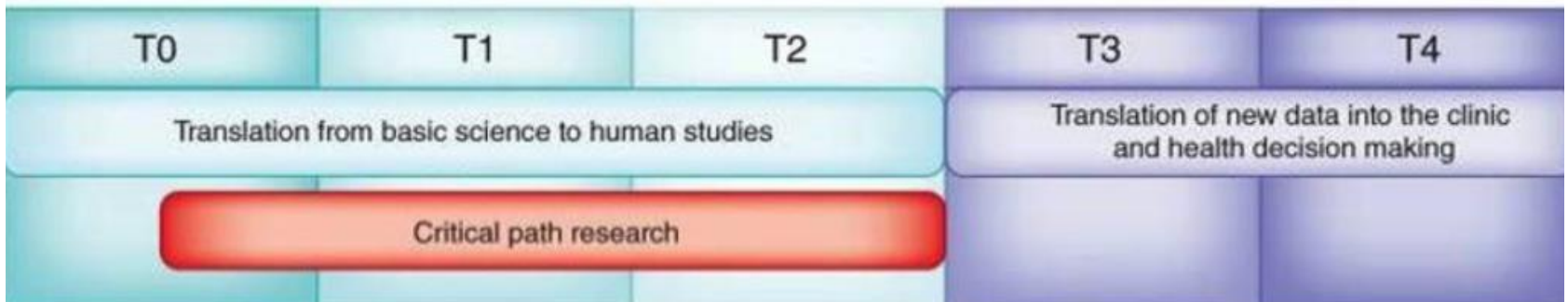
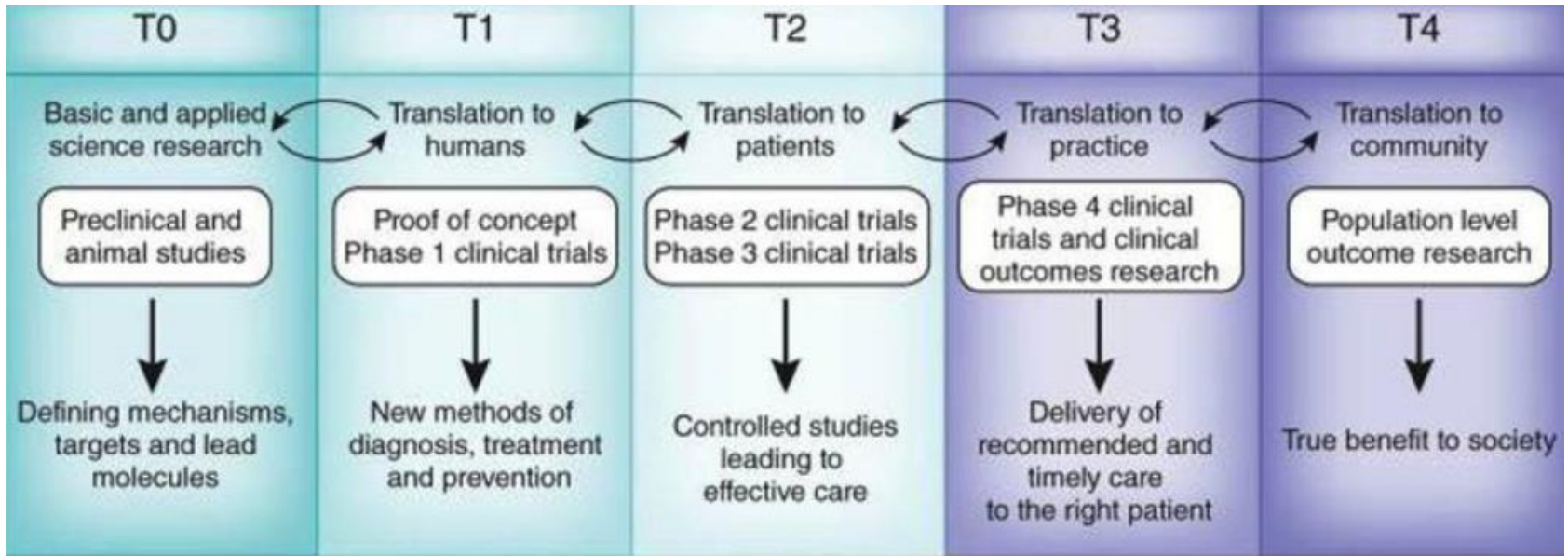
BY ROB ROGERS





# Increasingly relevant for patient benefit: Clinicians with insight into molecular mechanisms of disease

- increasing therapy complexity
- personalized approaches



# Acknowledgements

## Department of Medicine II, JLU

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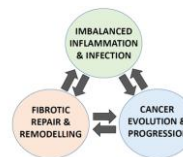
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## JLU-Career

Clinician-Scientist Program



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VIRUS-INDUCED LUNG INJURY

