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

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)
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.

Cassini et al, Euro Surveill, 2018
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.....

- 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
Unkel et al, J Clin Invest, 2012

Salwig et al, EMBO J, 2019
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.
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

1,018 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
Preclinical disease modeling: Developing a MERS-CoV in vivo model

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

- necrotizing, bronchointerstitial pneumonia
- alveolar edema
- hemorrhage


Dietert et al., *PLoS ONE*, 2017
Ongoing: Formulations for aerosolized deposition/compound modifications

Partner Site BREATH Hannover

- Compound modifications
- Aerosolized deposition
- (Inhalation) toxicology
- .......
- First-in-man
Successful translational pipeline for lung therapeutics established at the UGMLC

Discovery & Proof of concept
- Nanoparticle-based paclitaxel for PH: Nat Med 2014
- DNAzyme (asthma/COPD rhinovirus): JACI 2019, AJRCCM 2009, JCI 2012
- Inhaled GM-CSF for pneumonia-induced ARDS

Preclinical Development
- AJRCCM 2005
- Circulation 2006, ERJ 2008
- ERJ 2009, 2010
- NEJM 2005, AJRCCM 2010
- JCI 2005
- NEJM 2013 (starting 2019), Phase IIa (funded)
- EP17189860 2017
- Phase II (ongoing)
- AJRCCM 2014

Phase I/II
- JACC 2001, JACC 2006a/b
- Circulation 2006, ERJ 2008
- ERJ 2009, 2010
- NEJM 2013a, NEJM 2013b, Lancet 2016a, Lancet 2016b
- Circulation 2013
- NEJM 2015
- Phase I (ongoing)
- Phase IIa (funded)
- Phase II (ongoing)
- Phase II (completed)

Phase III
- NEJM 2002, JACC 2010
- NEJM 2005, Circulation 2009
- NEJM 2013a, NEJM 2013b, Lancet 2016a, Lancet 2016b
- Circulation 2013
- NEJM 2015
- Phase I (ongoing)
- Phase II (ongoing)
- Phase II (completed)

Approval
- IEU 2004/USA 2005 (iloprost) USA 2010 (treprostinil)
- EU/USA 2005 (sildenafil)
- EU/USA 2010 (tadalafil)
- EU/USA 2014 worldwide (riociguat)
- EU/USA 2015 (sildenafil)
- IEU 2004/USA 2015 (sildenafil)
- IEU 2013 (sildenafil)
- EP17189860 2017
- EP17189860 2018
- EP17189860 2019
- EP17189860 2020
Beyond viral pneumonia: sCAP and sCAP-associated Acute Respiratory Distress Syndrome

"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

Macrophage Tumor Necrosis Factor-α Induces Epithelial Expression of Granulocyte-Macrophage Colony-stimulating Factor
Impact on Alveolar Epithelial Repair

Am J Respir Crit Care Med, 2009

Lidija Cakarova¹, Leigh M. Marsh¹, Jochen Wilhelm², Konstantin Mayer¹, Friedrich Grimminger¹, Werner Seeger¹, Juergen Lohmeyer¹, and Susanne Herold¹
GM-CSF mediates lung (alveolar) epithelial cell proliferation and restoration of lung barrier function

LPS 50μg / 2.5x10⁴ K.pn. it

wt
GM-CSF⁻/⁻
SPC-GM

GM-CSF⁻/⁻ with constitutive alveolar overexpression of GM-CSF

Cakarova et al, AJRCCM, 2009
AEC II expressed GM-CSF increases survival after influenza virus (IV) infection

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

Unkel et al, J Clin Invest, 2012
Summary of findings on GM-CSF effects in pre-clinical animal models

- **Influenza virus**
  - CD103+ DC
  - Migration
  - Local expansion
  - Host defense
  - K. pneumoniae
  - Gram+ gram
  - Antigen-specific CD8+ T cells
  - Viral clearance

- **GM-CSF**
  - Epithelial progenitor
  - Proliferation
  - Restored barrier function
  - Injured alveolus

- **Restored barrier function**
  - Unkel et al, J Clin Invest, 2012
  - Schäfer et al, unpublished
  - Cakarova et al, AJRCCM, 2009
  - Unkel et al, J Clin Invest, 2012
  - 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
GM-CSF inhalation as compassionate treatment in severe CAP-associated ARDS

→ Bedside-to-Bench

### Phenotype Disease-Area (# patients) – DZL Biobank

<table>
<thead>
<tr>
<th>Disease-Area</th>
<th># Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma and Allergy (AA)</td>
<td>1610</td>
</tr>
<tr>
<td>Benign lesions</td>
<td>506</td>
</tr>
<tr>
<td>Bronchopulmonary Dysplasia (BPD)</td>
<td>141</td>
</tr>
<tr>
<td>Cancer</td>
<td>4687</td>
</tr>
<tr>
<td>COPD</td>
<td>4059</td>
</tr>
<tr>
<td>Cystic Fibrosis (CF)</td>
<td>374</td>
</tr>
<tr>
<td>Diffuse parenchymal lung dis. (DPLD)</td>
<td>3340</td>
</tr>
<tr>
<td>End stage lung disease (ESLD)</td>
<td>322</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>152</td>
</tr>
<tr>
<td>Pneumonia/ARDS</td>
<td>12431</td>
</tr>
<tr>
<td>Pulmonary Hypertension (PH)</td>
<td>1703</td>
</tr>
<tr>
<td>Tuberculosis (TB)</td>
<td>164</td>
</tr>
</tbody>
</table>
GM-CSF inhalation activates macrophages and improves oxygenation in CAP-associated ARDS (n=6)

pulmonary macrophage activation

CD80 (M1) and HLA-DR (MHCII) MFI (log fold increase of d-1) in GM-CSF and untreated groups.

oxygenation

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

Herold S et al, AJRCCM 2014
Lost in translation? Death valley No 1…

- 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

**Inclusion:**
CAP/HAP-associated ARDS with no clinical improvement under standard treatment

**Primary endpoint:**
Activation profile of pulmonary macrophages

**Secondary endpoints:**
Oxygenation, extravascular lung water, morbidity scores, days on ventilator/vasoactive drugs/alive, safety
...but a rapid ending

withdrawal of support of ARDS program upon stock market launch

- 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
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

![Translational pipeline diagram]

- Discovery & Proof of concept
  - Inhaled iloprost & inhaled treprostinil
  - Phosphodiesterase 5 inhibitors
  - Soluble guanylate cyclase stimulator
  - Tyrosine kinase inhibitor imatinib (inhaled/systemic)
  - Nanoparticle-based paclitaxel for PH
  - DNAzyme (asthma/COPD, rhinovirus)
  - Inhaled GM-CSF for pneumonia-induced ARDS

<table>
<thead>
<tr>
<th>Discovery &amp; Proof of concept</th>
<th>Inhaled iloprost &amp; inhaled treprostinil</th>
<th>Phosphodiesterase 5 inhibitors</th>
<th>Soluble guanylate cyclase stimulator</th>
<th>Tyrosine kinase inhibitor imatinib (inhaled/systemic)</th>
<th>Nanoparticle-based paclitaxel for PH</th>
<th>DNAzyme (asthma/COPD, rhinovirus)</th>
<th>Inhaled GM-CSF for pneumonia-induced ARDS</th>
</tr>
</thead>
</table>
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
Increasingly relevant for patient benefit: Clinicians with insight into molecular mechanisms of disease

- increasing therapy complexity
- personalized approaches

![Diagram of the translational research process from basic science to clinical practice](image-url)
Acknowledgements

Department of Medicine II, JLU
Christin Peteranderl
Lidija Cakarova
Theresa Schäfer
Ivonne Vazquez-Armendariz
Monika Heiner
Stefanie Jarmer
Larissa Hamann
Nicole Tewes
Carmen Schade-Brittinger
Janina Trauth
Jürgen Lohmeyer
Dieter Walmrath
Werner Seeger

MPI for Heart & Lung Research, Bad Nauheim:
Thomas Braun, Isabelle Salwig

Sequencing and Bioinformatics Core, JLU:
Jochen Wilhelm, Torsten Hain, Jan-Philipp Mengel, Alexander Goesmann, Andreas Hoeck

Department of Veterinary Pathology, FU Berlin
Achim Gruber
Kristina Dietert

DZIF/PU Marburg:
Stephan Becker
Lucie Sauerhering

Northwestern U Chicago, Pulmonary & Critical Care
GR Scott Budinger,
Iasha J. Sznaijd