Bundesinstitut für Impfstoffe
und biomedizinische Arzneimittel

Paul-Ehrlich-Institut

www.pei.de

IPFA/PEI 27th International Workshop on Surveillance and Screening of Blood-borne Pathogens

04 -06 May 2021 (Virtual)

Session 3: Passive Immunotherapies

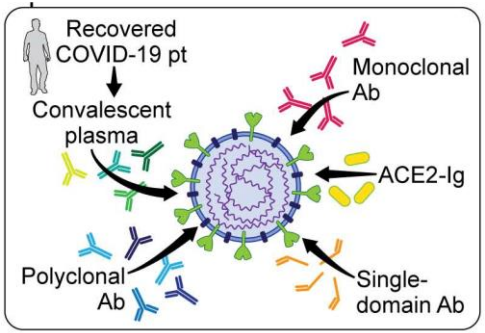
Monoclonal and Polyclonal Antibodies

Steffen Gross,
Head Section monoclonal - and polyclonal Antibodies
Paul-Ehrlich-Institut
Germany

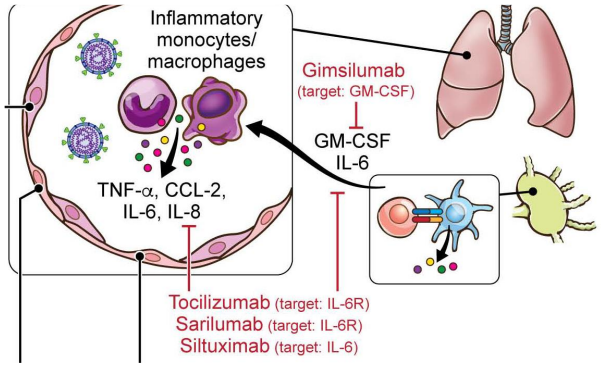
Das Paul-Ehrlich-Institut ist ein Bundesinstitut im Geschäftsbereich des Bundesministerium für Gesundheit

The quest for Covid-19 biomedicinal therapeutics

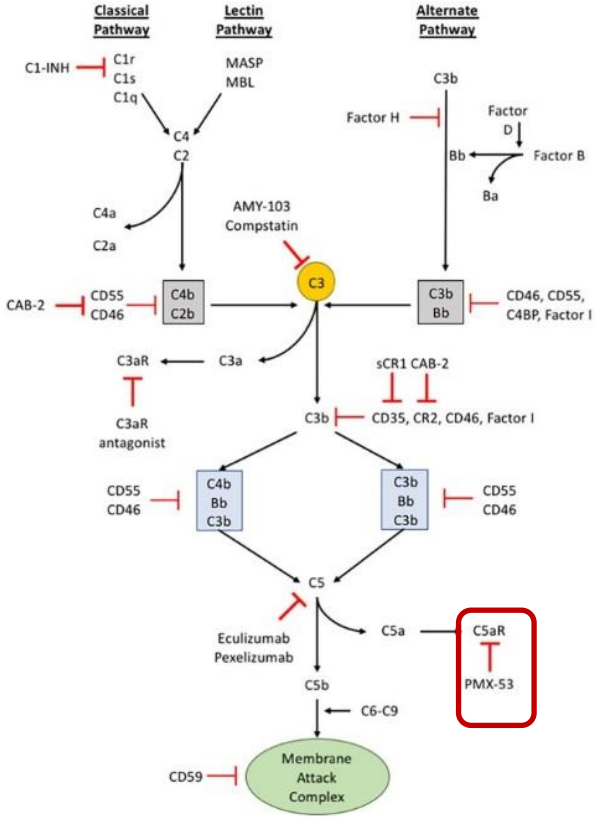
- „Re-purposing“ and symptomatic/anti-inflammatory treatment
  - Anti-IL-6, anti-IL-6R, anti-C5a, anti-C5….
- Hyperimmunoglobulins
  - CP, Plasma fractionation, plasma industry alliance
- Anti-COVID 19 Therapeutic Biologics
  - Anti-Spike/RBD antibodies (Cloning of antibodies from recovered patients)
  - Immunosera from immunized animals
  - ACE-IgG-Fc-fusions
  - …..

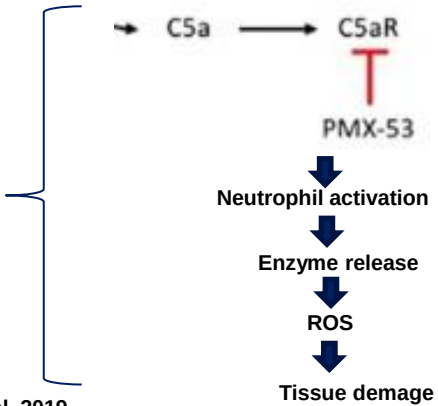


Approaches for symptomatic treatment



Vabret et al, Immunity 2020
https://doi.org/10.1016/j.immuni.2020.05.002





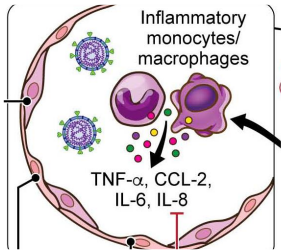
Emily et al., Fron Immunol. 2019

„Re-purposing“ and symptomatic/anti-inflammatory treatment

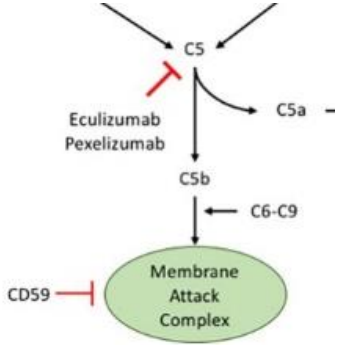
Clinical trials

- Phase III:randomized, double-blind, placebo-controlled trials to assess the efficacy and safety in combination with Standard of Care in hospitalized adult patients with severe COVID-19 pneumonia.

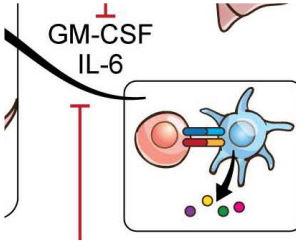
- anti-IL-6/IL-6R



- anti-C5/C5a



- Anti-GM-CSF

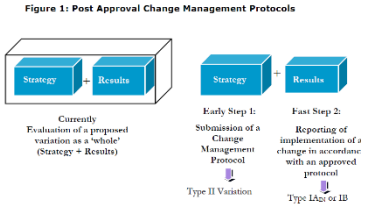


- Adrenomedullin…..

Issues and mitigations (ECMP)

Supply issues:

- Upscale and/or additional manufacturing sites
- Challenge: Submission and time to approval



Regulatory flexibility

- Mechanisms for post-authorisation change management (i.e. PACMP and accelerated timelines/expedited review

- exceptional change management process (ECMP) is made available to MAHs of crucial medicines for treatment of COVID-19 patients.
  - Within two working days, the MAH will be informed whether the relevant competent authority has agreed to the application of the ECMP.
  - submit the corresponding variation application to the competent authorities no later than within 6 months following the implementation of the change.

Media releases - initial results

29.07.2020
Roche announced that the phase III COVACTA study of Actemra®/RoActemra® (tocilizumab) did not meet its primary endpoint of improved clinical status in hospitalised adult patients with severe COVID-19 associated pneumonia. There was no statistically significant difference in the distribution of clinical status (ordinal scale) at day 28 between the treatment groups

10 March 2021
The REMDACTA clinical trial of Actemra plus Veklury did not meet its primary endpoint of improved time to hospital discharge for patients with severe COVID-19 pneumonia or its key secondary endpoints compared to Veklury alone

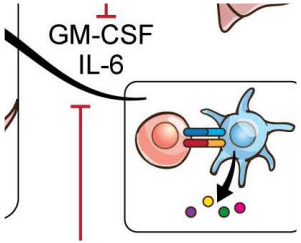
01.09.2020
Sanofi today announced that the global Phase 3 trial investigating intravenously administered Kevzara® (sarilumab) at a dose of 200 mg or 400 mg in severely or critically ill patients hospitalized with COVID-19 did not meet its primary endpoint and key secondary endpoint

Research and Studies ongoing

18 September 2020

Roche's phase III EMPACTA study showed Actemra/RoActemra reduced the likelihood of needing mechanical ventilation in hospitalised patients with COVID-19 associated pneumonia

- EMPACTA is the first global phase III trial to show efficacy with Actemra/RoActemra in COVID-19 associated pneumonia and the first with a focus on enrolling largely underserved and minority patients
- There was no statistical difference in mortality between patients who received Actemra/RoActemra or placebo

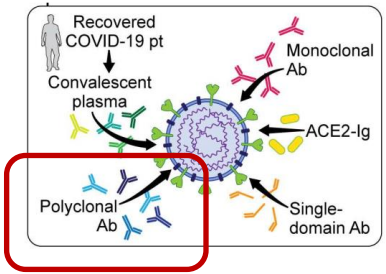


29 February 2021

GlaxoSmithKline plc (LSE/NYSE: GSK) announced results from the phase 2 proof of concept OSCAR (Otilimab in Severe COVID-19 Related Disease) study with otilimab, an investigational anti-granulocyte macrophage colony-stimulating factor (anti-GM-CSF) monoclonal antibody.

During the 28-day follow-up, death occurred in 0% (n=0/13) of mavrilimumab recipients and 27% (n=7/26) of comparison-group subjects, 100% of mavrilimumab recipients and 65% of comparison-group subjects achieved clinical improvement (defined as an increase of ≥ 2 categories on a 7-point WHO clinical status scale

Hyperimmune globulins



Plasma

- Donors
- Access and analysis of hyperimmune sera
- Screening
- Anti-virus Titer!

Fractionation

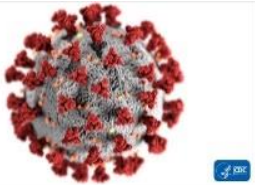
- Manufacturing Process
- Process/Product characterisation
- Potency assay
- Release
- Stability

Clinic

- Named patient program
- Compassionate-Use
- Clinical trial
  - placebo-controlled
  - in combination with SOC
  - Protective titer determination

Recommendation of the Paul-Ehrlich-Institut for the Collection and Manufacture of COVID-19 Convalescent Plasma

For the use of COVID-19 convalescence plasma outside clinical trials and for its use as a starting material for the production of specific immunoglobulins, the following criteria should be considered.
In principle, for the donor selection in order to produce COVID-19 convalescence plasma all requirements for plasmapheresis donors of the current national guidelines on haemotherapy as well as the requirements of the Paul-Ehrlich-Institut are prerequisites.



In addition, the following specific requirements apply:

- Admission to donation: 4 weeks after complete recovery from COVID-19 or 2 weeks after the last negative SARS-CoV-2 PCR diagnosis from a smear.
- The person willing to donate has tested positive for antibodies against SARS-CoV-2
- In addition to the requirements of Section 10 of the German Medicines Act (Arzneimittelgesetz, AMG), COVID-19 convalescence plasma must be labelled as such

Testing of SARS-CoV2 antibodies should be implemented at least at plasma mini pools, at intermediates and final product

Issues on CMC approach for IgG/H-IgG

- globally sourced non-PMF plasma for the manufacture
  - comply with the EU regulation regarding donor selection, this has to be in accordance with the donor requirements in Directive 2004/33/EC

- for non-PMF collection centers, inspections will be conducted by National Competent Authorities (NCAs)?
  - acceptable for European blood banks/transfusion centers in the EU inspected by the Member States NCAs according to the EDQM/EC Good Practice standards
  - adequacy of this approach for the inspection of non-PMF plasma centers located outside the EU?

- Hyperimmune product QTPP and potency assay development
  - characterize the anti- SARS-CoV-2 specific titer in each HI-G lot prior to release to the clinical trial
  - Other QA: IgG composition, impurities etc.
  - Comparability

Plasma Alliance

News Release

GLOBAL PLASMA LEADERS COLLABORATE TO ACCELERATE DEVELOPMENT OF POTENTIAL COVID-19 HYPERIMMUNE THERAPY

– *Partnership brings together world-leading plasma companies to focus on developing and delivering a hyperimmune immunoglobulin in the global fight against COVID-19*

Topline Results from NIH-Sponsored Clinical Trial of Investigational COVID-19 Hyperimmune Globulin Medicine

CoVIg-19 PLASMA ALLIANCE

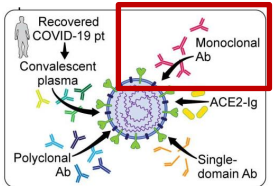
Working Together to Fight COVID-19 with Immunoglobulin (Ig) Therapy

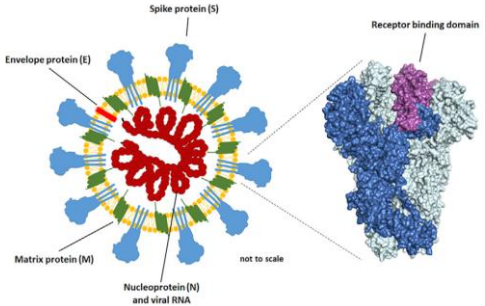
Phase 3 Inpatient Treatment With Anti-Coronavirus Immunoglobulin (ITAC) Clinical Trial Sponsored and Funded by the National Institute of Allergy and Infectious Diseases (NIAID), Part of the National Institutes of Health (NIH),

April 2, 2021 – The CoVIg-19 Plasma Alliance today announced that the Phase 3 Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC) clinical trial sponsored and funded by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), did not meet its endpoints.
No serious safety signals were raised in the trial.

Anti-COVID-19 Therapeutic mABs(-derivatives)

- Target
  - SARS-CoV-2 S protein engaging ACE 2 as the entry receptor
- Sources
  - isolated from animals immunized with spike proteins
  - patient-derived (phage display libraries…)
- Formats
  - optimal affinity, manufacturability, lower immunogenicity risk
  - Reduced effector function (ADCC/CDC) for optimal safety (no ADE)
  - Extented $t_{1/2}$
  - IgG1 /Fc-silenced; IgG4, Nanobodies…
  - ACE-IgG-Fc-fusion
- Challenges
  - Speed to get the drug to patients
  - Manufacturing process development (cell lines, viral safety, Titer, characterisation of product)
  - animal models (transgenic mice, hamster, ferret…)
  - clinical trials
  - patient population (severe, mild, prophylaxis?)
  - Dose finding





Structure of Coronavirus Particle (from Amanat et al, 2020)

Common questions on CMC approach

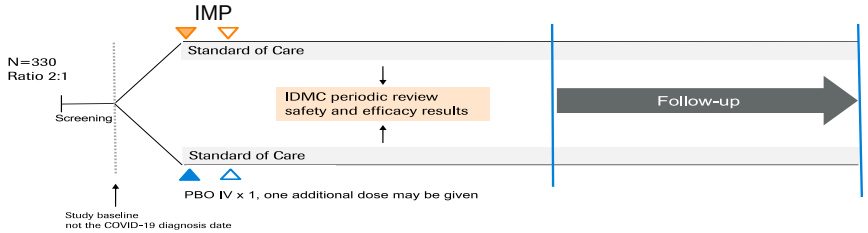
- Use of cell pools (e.g. isogenic cell lines/cell pools to produce anti SARS CoV-2 antibodies for clinical trials
- Adventitious agents safety data package required in the CTA for initiation of clinical trials
- Comparability/Validation
- Prior knowledge/platform knowledge
- IMPD with only release data and stability data on the non-GMP pilot batch

Anti-SARS-CoV2 also time for collaboration

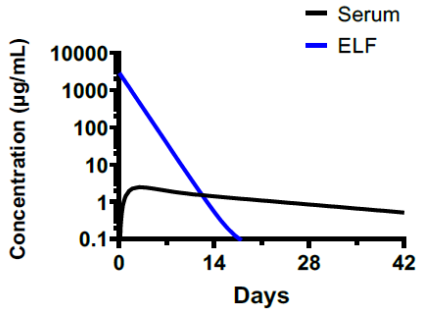
- Regeneron/Roche
  - REGN-CoV2 (casivirimab/imdevimab)
- GSK/Eli Lilly
  - Bamlanivimab
  - Etesivimab (Bamlanivimab/Etesivimab)
  - VIR-7831
  - Bamlanivimab/VIR-7831 (Eli Lilly,Vir Biotechnology, Inc. and GSK)
- Celltrion
  - Regkirona (CT-P59)
- University/Research centres/experienced manufacturer(s)….

Clinical challenges

- Phase III: randomized, double-blind, placebo-controlled trials to assess the efficacy and safety in combination with SOC
  - in hospitalized adult patients with severe COVID-19 pneumonia.
  - ….



- Prophylactic vs. Therapeutic setting
- Patient population
- Endpoints (virus load vs. Clinical endpoints)
- Mono- vs. Combinationtherapy
- Resistance and escape mutants
- ADE
- Interference with Vaccination?
- Route of administration (iv vs. inhalation, formulation development



Activities to enable/accelerate patient access

- Timely National scientific advice with multiple Stakeholders
- Ad Hoc teleconferences/advices
- Rapid Scientific Advice by EMA
- Article 5(3) procedures (and updates?)
- MAA (rolling review, accelerated procedures)
- Accelerated review of variations
  - Expedited Review: Variations associated with extents manucaturing capacities (up-scale, new sites…
  - New: exceptional change management process (ECMP)
  - Extension of Indications (EoI, for approved products)
- Potential Drug shortage mitigation
- Advice to Minstry of Health, public relations, …

Thank You!


Paul-Ehrlich-Institut
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Aktuelle Infos auf einen Blick: z.B. PRAC-Sicherheitsbewertung, STIKO-Empfehlung, Aufklärungsmerkblatt für Impfwillige, Infoblatt für Ärzt:innen
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