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HERRENHAUSEN SYMPOSIUM

HERRENHAUSEN PALACE, HANNOVER

SUMMARY REPORT

"INDIVIDUALIZED INFECTION MEDICINE – THE FUTURE IS NOW"

Infections continue to be amongst the main causes of death throughout the world. New and recurrent infectious diseases, combined with steadily increasing resistance to antibiotics and the global mobility of people, create enormous new challenges for modern medicine. Consequently, therapies must combine maximum efficacy with minimum side effects. Customized strategies for prevention and clinical management are increasingly gaining in importance in this context.

In oncology for example, therapies tailored for the individual patient and his or her specific tumor, are already being applied successfully today. However, the promising potential of individualized therapies has hardly been tapped yet in the field of infectious diseases. In order to precisely control diagnostic clarification and therapeutic intervention in the future, new technologies need to be developed and the existing knowledge needs to be merged.

During the Symposium "Individualized Infection Medicine – The Future is Now" from June 21-23, 2018 leading experts from science, medicine and pharmaceutical industry as well as representatives of important initiatives in the field of personalized medicine from all over the world gathered at Schloss Herrenhausen in Hannover, Germany, and reviewed current trends and developments. In seven sessions and two panel discussions focusing on different aspects in personalized medicine as well as five lightning talks from travel grantees and almost 50 poster presentations recent developments in the field of individualized infection medicine were discussed. In addition developments in other fields of personalized medicine were reviewed that might have an impact on the diagnosis and treatment of infectious diseases in the future with a particular emphasis on individualized infection medicine.

Individualized Medicine – Today and Tomorrow

Edward Abrahams (Washington, USA), in his keynote talk, gave an overview on the concept of individualized medicine and presented how certain personalized approaches are already improving health care. Examples of breast cancer and stroke prevention showed that genetic testing prior to treatment has a major impact on the outcome and/or costs. Abrahams explained that health care is rapidly transforming, not at least shown by the steadily increasing numbers of personalized medicine approved by the FDA. The role of the patient but also the health care provider will change and new demands on and from the payers emerge. Abrahams appealed to combine efforts to meet these challenges and to overcome the barriers to realize personalized medicine.

In the following keynote talk, **Hagen Pfundner** (Grenzach-Wyhlen, Germany) stated that personalized medicine is guided by an overarching principle, the molecular information. This is valid for all fields of medicine including oncology, where the value has already be proven, but also infection medicine. For advancing personalized medicine key competence in cutting-edge molecular diagnostics, digital technologies, data management and science as well as pharmaceutical research and development will need to be developed and integrated. Flatiron studies showed the potential of real-world evidence to be used in innovative and high-impact ways, ultimately accelerating the time it takes to get the most effective therapies into the hands of patients. Pfundner called for establishing a meaningful data base which will fundamentally change clinical development and trial design.

Nisar Malek's (Tübingen, Germany) presentation focused on how personalization can be integrated in today's clinical practice. Within the creation of the center for personalized medicine in Tübingen a role model is currently built up, which is organized around competences and not clinical entities. This allows adaption to changes arising from clinical and experimental challenges and will allow integration of personalization to different fields of medicine. Malek underlined that implementation requires institutional changes, large scale collaboration, changes in the health insurance systems especially in reimbursement policies and education of the public and patients.

Matthias Löhr (Stockholm, Sweden) presented work on how artificial intelligence can support personalized medicine by transforming available information into meaningful data. The 'Dataome Technology Platform' captures, integrates and links quality assured global data and knowledge about interventions, outcomes and molecular mechanisms and thus empowers the transformation of clinical and molecular data into evidence-driven decision support and real-life healthcare applications.

Paul Kellam (London, UK) described the influence of host and pathogen genetic variations on virulence, transmission and outcome and the potential for disease stratification. Their work showed that different non-coding polymorphisms in interferon inducible transmembrane proteins (IFITM) are associated with severity of influenza. Such knowledge now needs to be transformed to a complex understanding of the underlying genetics to stratify people having a genetic predisposition for a more complicated or severe course of disease and leverage new treatment modalities or targeted preventive therapies.

Christoph Klein (Munich, Germany) shared insights into the peculiarities of pediatrics. Childhood death is often linked to infections and on a global scale doesn't require precision medicine per se but more importantly access to treatment. In industrialized countries, however, a large number of cases are due to inborn defects in the immune system. Such rare diseases require precision medicine including the application of novel diagnostic tools and personalized therapies.

Infections are a major threat after stem cell transplantation, but the current treatment options are not satisfactory. **Tobias Feuchtinger** (Munich, Germany) introduced the adoptive T cell transfer of

antigen-specific T cells as second line treatment of viral infections after stem cell transplantation and called for controlled studies to prove efficacy of this physiologic and individualized treatment approach.

Requirements for Advancing Individualized Medicine

In his keynote, **Otmar Wiestler** (Berlin, Germany) focused on the major challenges for personalized medicine, namely converting big to smart data, bridging the gap from preclinical to clinical translation and educating clinicians and scientists to be able to apply the new concepts. The Helmholtz Association meets this challenge with its translational centers combining technology and concept platforms with interdisciplinary experts under one roof. In addition, projects within the Helmholtz Personalized Medicine Initiative "iMed" or the Proof-of-Concept Initiative help implementing alliances between the different players which are essential to explore this challenging area.

Keith Stewart (Phoenix, USA) highlighted in his keynote the importance of clinical genomic testing and the steadily rising numbers at Mayo Clinics bringing precision medicine to bedside. But still many barriers exist to deliver it, e.g. the turnaround time, FDA readiness and insurance coverage. On the other hand, genomics information can already today be leveraged in pharmacogenomics. In 99 percent of individuals having their genome sequenced actionable pharmacogenomic information is found, which can be used to determine if prescribing is safe and effective. Stewart argues for implementation of a pharmacogenomic alert if certain drugs are ordered.

Martin Krönke (Cologne, Germany) reviewed the current state of personalization in vaccinology, which is mainly distinguishing "when" a vaccine is given, determined by age and "if" a vaccine is given, determined by medical pre-condition and risk. However, the immune responses to a given vaccine in a certain dose differ due to genetic and non-genetic factors. Krönke concluded that vaccine antigen selection should be optimized, pathogen-derived peptides should either broadly bind different HLA-molecules or need to be tailored, genetic factors influencing the immune response need to be considered and new adjuvants to overcome corresponding limitations should be utilized in vaccine design.

In the subsequent **panel discussion** with **Edward Abrahams, Martin Krönke, Keith Stewart and Otmar Wiestler** chaired by **Ulrich Kalinke** (Hannover, Germany), it was mutually concluded that collecting evidence for the efficacy of personalized medicine and proving its value, both in terms of economics and benefit for the society, will be critical. To reach this, standardization and cooperation across disciplines and borders will be crucial. In addition, education was seen important for the success of personalized medicine. This includes teaching the people in the healthcare system to exploit the developing new tools to leverage the complex data sets arising, but also education of the public.

Approaches For Individual Prevention And Treatment On Infectious Diseases

Eric Pamer (New York, USA) presented in his keynote talk that the complex microbial networks in the gut provide colonization resistance, but that the direct and indirect mechanism remain incompletely understood. He shared data showing that the microbiota diversity predicts the survival after allogeneic hematopoietic stem cell transplantation. In a randomized trial of auto-fecal material transfer (FMT) in allo-stem cell transplantation this finding is currently tried to be implemented for the benefit of the patients. Pamer further envisioned that reconstitution of mucosal bacterial populations following e.g. antibiotic therapy using FMT or specific commensal microbes provides an alternative approach to treat and prevent infections in an era of decreasing antibiotic susceptibility.

Till Strowig (Braunschweig, Germany) focused on the importance of preclinical microbiome models to develop personalized approaches. Due to the complexity of the system and limited knowledge of co-factors the old question of "cause or consequence" cannot be easily answered in terms of alterations in the microbiota. And even though the findings of differences in the microbiota are likely to be the cause, it is still hard to predict how to interfere. Strowig presented examples how preclinical mouse models can bridge the gap between cohort findings and future intervention studies.

Dietmar Pieper (Braunschweig, Germany) presented that the clinical effectiveness of FMT for treatment of recurrent Clostridium difficile infections has been demonstrated in randomized controlled trials and that various studies are ongoing to test the effectiveness of FMT in e.g. metabolic syndrome, obesity, food allergies and inflammatory bowel disease. Pieper shared results from an FMT-study in chronic antibiotic-refractory pouchitis which proved FMT as treatment option, even though the underlying organisms and metabolic pathways still need to be elucidated. This underlines the urgent need of clinical trials assessing the efficiency of FMT but also identifying correlations between microbial metabolism and health outcome.

What determines the variable responses to viral respiratory tract infections and why do some develop mild disease while others suffer a severe disease course? **Peter Openshaw's** (London, UK) group is trying to answer those questions by studying intensively the host response in human infection challenge studies. Openshaw shared results from human pH1N1 and RSV challenge studies. So far those have been safe and allow for multiple compartment sampling in standardized conditions which promise a greater understanding of the underlying mechanisms determining severity.

Beate Kampmann (London, UK) stated that pediatrics per se is a forefront topic of individualized medicine as therapies often derive from adult protocols. However, integration of pediatrics into recent developments in e.g. genetics is suboptimal which needs to be changed. Childhood tuberculosis (TB) for example shows that individual characteristics as genetics, age and environment determine susceptibility and pathogenesis, however, the treatment schedule is still the same. Kampmann presented how the TB Child Multidrug-Resistant Preventive Therapy Trial (TB-CHAMP) is developing a biosignature to predict which child would most benefit from preventive therapy after exposure to MDR TB.

Steven Kern (Seattle, USA) discussed how individualized medicine might be also accessible within resource-limited settings. By shifting the focus from treatment to prevention, improving early detection of pathogens and infectious disease outbreaks and modernizing public health surveillance, epidemiology and information systems, precision public health could be established. Kern showed examples in which mass drug administration (MDA) campaigns were combined with screening campaigns to identify patients with certain co-infections that are in need to specific regimens. Also, malnutrition needs to be considered as it may influence drug metabolism and thus the drug dose needed or alternatively a high-fat meal might be co-administered with the drug.
Diagnostics for Individualized Infection Medicine

In his keynote, **Christopher Woods** (Durham, USA) showed that the emergence of antimicrobial resistance is driven by our inability to more precisely identify the cause of infection and the likelihood of progression. Wood's group studies how the host response measured by various 'omics' and combined with phenotypical data can be utilized to develop multi-dimensional predictive models of health and disease to inform clinical decision making in infectious diseases. By means of machine learning a pan-viral transcription classifier was developed which is capable of strong and early separation of those who will become sick from those who remain well, supporting a public health approach for early detection that would allow early effective treatment, reduce viral transmission and thereby mitigating an epidemic.

Susanne Häußler (Hannover, Germany) further elaborated how targeted treatment could fight antimicrobial resistance. Today's microbial diagnostics is restricted and delayed and leaves the physician with uncertainty about which drug best to prescribe and thereby contributes to the spread of resistant pathogens. To overcome this shortness Häußler's group is developing faster diagnostic tests based on the least number of informative single nucleotide polymorphisms that unambiguously identify resistance in bacteria. A panel of molecular markers tested in clinical Klebsiella pneumoniae isolates with the RAPID MassARRAY, predicted resistance fast and accurately and may also be used to identify clonal nosocomial outbreaks.

Alice McHardy (Braunschweig, Germany) explained how bioinformatics can be exploited to infer genotype-phenotype and genotype-environment associations from microbial omics data. McHardy's work concentrates on different methods which can be applied to omics data to predict models, detect biomarkers or allow tree inference. Examples shown include TRAITAR, that combines machine learning with evolutionary modelling to predict microbial phenotypes, and Seq2Geno2Pheno, that predict sensitivity or resistance from molecular markers as shown by Susanne Häußler. Such methods will enable personalized medicine, e.g. for antimicrobial diagnostics or microbiome-related conditions.

Data Science in Individualized Infection Medicine

Osmar Zaïane (Edmonton, Canada), in his keynote, explained the vision how artificial intelligence can be used in medicine and gave an overview on the overarching topic. The sub-theme machine-

learning comprises processes that provide algorithmic means to learn from large data, interpret the trends in the data and adapt to the data. This includes the field of supervised learning which is mostly known for the sub-topic deep learning. Zaïane argues that the use of machine learning will be key to improve effectiveness in health care through personalization. On the example of Ebola virus infection he showed how artificial intelligence can predict disease propagations, identify possibly infected individuals and reduce the risk of Ebola spread within a community or geographic location. On the other hand, it also can be used to score drugs as potential inhibitors for such outbreaks helping prioritize compound testing.

Fabian Theis (Munich, Germany) continued illustrating the potential of machine learning for understanding how individual differences impact health. Starting from the example of predicting cell cycle by the use of machine learning to order on singe cell level by similarities, he explained how this idea can be used to breakdown disease progression in greater detail as it is currently possible and thereby will help to intervene much earlier. This technique, however, will not give any insights in the underlying mechanistic, wherefore his team is also working on dynamic models summarizing molecular interactions underlying those statistical links. Finally, Theis highlighted the importance of cells as basis for the understanding of individualization and summarized the efforts undertaken to reach a human cell atlas.

Thomas Illig (Hannover, Germany) highlighted the potential as well as the need of biobanks. The fact that 50% of preclinical research is not reproducible is in part due to the non-standardized and non-quality-controlled storage of biosamples. However, to identify molecular markers suitable for personalized medicine reproducibility is key. Regional, national and international alliances emerge establishing defined, documented and reproducible processes with quality management structures and high quality of samples and corresponding data. Illig shared examples showing that such modern and innovative biobanking allows search for biomarkers even though those differ on conditions like gender, age, disease or life style.

Treatment and Prevention in Viral Infections

According to the WHO global hepatitis report 2017 viral hepatitis has surpassed other viral infections as cause of global annual mortality. In his keynote, **Ralf Bartenschlager** (Heidelberg, Germany) summarized the history of hepatitis C treatment from the 1980s until today and explained how the individualized treatment in the beginning was step by step standardized and finally ended in a ‘one pill fits all’ strategy. Even though this development is contrary to many other fields this might be key to reach global elimination. However, Bartenschlager emphasized that the global eradication of hepatitis C virus will hardly be possible without the development of an effective vaccine and that in the era of potent antiviral therapy still many challenges remain unanswered.

Markus Cornberg (Hannover, Germany) introduced the current challenges in chronic hepatitis B treatment. Even though potent treatment options are at hand, cure is still not possible. In addition, good stratification criteria are missing to decide who should get which treatment and when and if to

stop treatment is feasible. Cornberg called for a combination of host immune and viral biomarkers. This is especially becoming important as stopping treatment eventually can lead to HBsAg loss and thus could be utilized as new treatment option. Also, new treatment options based on new targets are near to market, increasing the need of evidence-based clinical decision making.

Heiner Wedemeyer (Essen, Germany) shared recent developments in treatment of the orphan hepatitis viruses caused by hepatitis D (HDV) and E (HEV). As HDV is the most severe form of viral hepatitis, it is crucial to identify patients at risk for disease progression. Wedemeyer's team could show that distinct cellular responses in patients correspond to the response to therapy. In addition, certain virological profiles were identified hinting to those patients likely to benefit from treatment. However, for the remaining patients, new treatment concepts are needed and Wedemeyer shared promising data for an entry inhibitor from a phase IIb trial. On the example of hepatitis E and the Ribavirin-treatment induced mutagenesis, Wedemeyer concluded that there are a variety of tools to manage viral hepatitis, but that the treatment decision need to be taken wisely in an individualized manner.

For HIV there is still neither a vaccine nor a cure available. **Michel Nussenzweig** (New York, USA) presented in his keynote groundbreaking work for the development of vaccines as well as new therapeutic concepts. Starting from the discovery that few patients develop effective neutralizing antibodies (nAb) but only after years of infection, Nussenzweig and his lab revealed that several rounds of somatic hypermutations lead to the broadly nAb (bnAb). Thus, an effective vaccine will need to follow a new concept of vaccine design using sequential immunogens. But even though Nussenzweig's teams could proof the concept in a mouse model, application in humans is still far away and will need simplification of the current concept. Thus, in the meantime passive therapy with existing bnAbs is further elaborated and Nussenzweig shared promising data from 200 patients enrolled in clinical studies using the bnAbs 3BNC117 and 10-1074 either alone or in combination. So far, no significant adverse effect was observed and based on the findings, such antibodies could be a viable substitute for the currently used drugs.

Treatment of HIV is a combinatorial challenge facing millions of HIV variants and over two dozen drugs. **Thomas Lengauer** (Saarbrücken, Germany) explained how artificial intelligence can be used to determine the best drug combination for an individual patient. By the use of data mining of over 170,000 therapy regimes the geno2pheno server was developed offering analysis of resistance phenotypes and subsequent recommendations for suitable drug combinations. The system was validated in many independent studies and is recommended by the German/Austrian and European Guideline for HIV therapy. Future work will focus on incorporation of more information to improve predictions and to help debias human decisions, but getting output also with less information to also serve the developing world.

Marylyn Addo (Hamburg, Germany) summarized the developments in HIV treatment over the years. Improved understanding of pathophysiology and pathogenesis has allowed for the development of better instruments in HIV therapy. Many developments are based on mechanistic findings in

individuals that are able to control HIV. Best known example is the resistance to HIV in Caucasians due to CCR5 mutations and subsequent CCR5-targeting drugs. Having a toolbox of drugs, virus analysis, immune tools and technology at hand dramatically increased individualized HIV management. Including more tools as pharmacogenomics will help tailoring antiretroviral therapy even more effectively.

Paving the Way for Individualized Infection Medicine

Christof von Kalle (Heidelberg, Germany) gave an overview on the state of the art of personalized oncology at the National Center for Tumor Diseases Heidelberg (NCT). Having installed interdisciplinarity, infrastructure, data integration, molecular diagnostics and standardized workflows integrating every patient and every trial the challenge is now to transform this into usable smart data and extend its reach. The available DataThereHouse helps NCT clinicians by displaying data from various sources for a comprehensive overview relevant for personalized treatment. In a next step a DataBox will be established as a patient-centered health data management system. This will allow the management of complex health datasets derived from different sources, provides access to patients' data in a central repository, accessible via smartphone app, e-mail or webtool. The tool will also allow to manage appointments and request records. Furthermore, anonymized basic datasets can be queried by certified institutions, in order to e.g. search for study candidates.

Heyo Kroemer (Göttingen, Germany) stated that the driving forces for personalized medicine are technological achievements over recent years and the drastic change in demography. Due to the latter, there will be an enormous pressure towards translation with systems medicine as a solution. Prerequisites for the realization are sophisticated technologies and analytics, improved IT solutions for big data and well designed cohorts to learn from. On the example of the Snyder lab study (Chen et al., Cell 2012), Kroemer concluded that integrative personal omics profiles are possible and will bring new insights but for clinical use data reduction is needed. He also calls for solutions to use and combine the different types of available big data, namely the conventional big data from omics and imaging, the currently unused big data in form of standard medical data and the private big data from wearables and smart devices.

In the concluding **panel discussion** with **Heyo Kroemer, Ansgar Lohse, Christof von Kalle and Christopher Woods** chaired by **Michael Manns** (Hannover, Germany), data access and privacy was discussed. There is common agreement, that existing data in the clinics but also from clinical trials or insurance companies should be made available for the benefit of the patients. It became clear that still many aspects especially with respect to data privacy need to be solved, but that national as well as international initiatives are paving the way to make per se available data better accessible. Another crucial aspect is the quality of available data sets and the expertise to use the modern technologies to analyze the data. The unanimous opinion was that training in this area must be strongly promoted. Furthermore, the current development will change the balance of power in medicine, which must be prepared.

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NOTE

All academic titles have been omitted.

HZI HELMHOLTZ Centre for Infection Research MHH Hannover Medical School CiiM VolkswagenStiftung