Translation and early phase research at MHH

ZKS & Early Clinical Trial Unit (ECTU)

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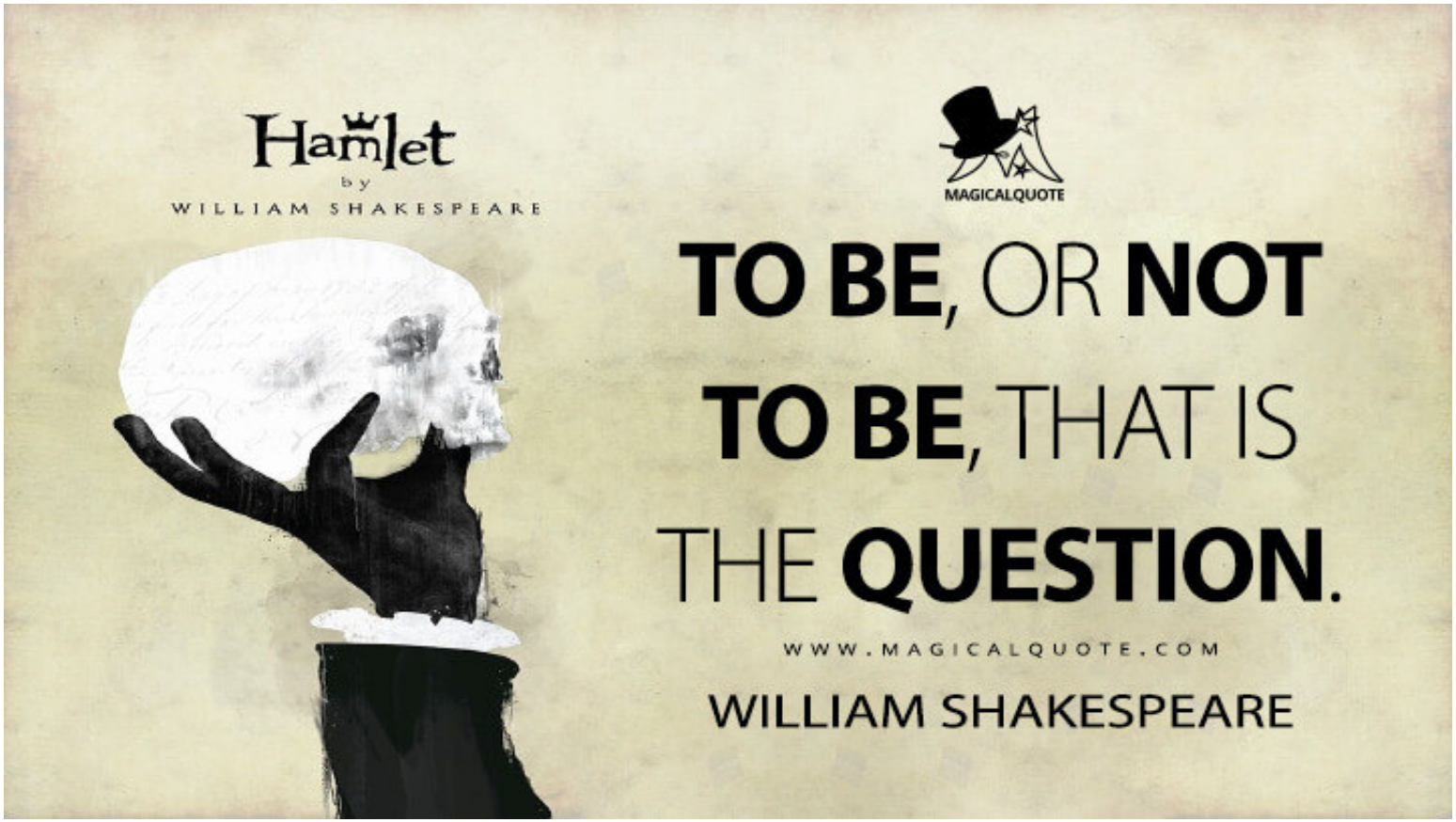
Hannover Medical School

Zentrum für Klinische Studien der MHH


Hamlet
by
WILLIAM SHAKESPEARE
MAGICALQUOTE
TO BE, OR NOT
TO BE, THAT IS
THE QUESTION.
WWW.MAGICALQUOTE.COM
WILLIAM SHAKESPEARE

Translational Medicine

- is a way **to overcome** the **extreme specialization**

- implies **evolution** in **thinking** and **organizing research centers**, especially also *university students*, in order to create a continuous flow of knowledge and bidirectional operation that goes ***from the laboratory to the bedside***.

- Root is the **collaboration** between various professionals, each skilled and specialized in their field, knowledge of which can certainly be transformed into an **added value** as well as **economic ensuring** concrete results in even shorter time.

Translational Medicine @ UniSa, - ISSN 2239-9747 2013, 5(3): 5-6

NIH Public Access
Author Manuscript
Transl Res. Author manuscript; available in PMC 2013 June 01.

Published in final edited form as:
Transl Res. 2012 June ; 159(6): 430–453. doi:10.1016/j.trsl.2011.12.009.

Translational research in infectious disease: current paradigms and challenges ahead

Judith M. Fontana, PhD[a], **Elizabeth Alexander, MD**[b], and **Mirella Salvatore, MD**[a,b]
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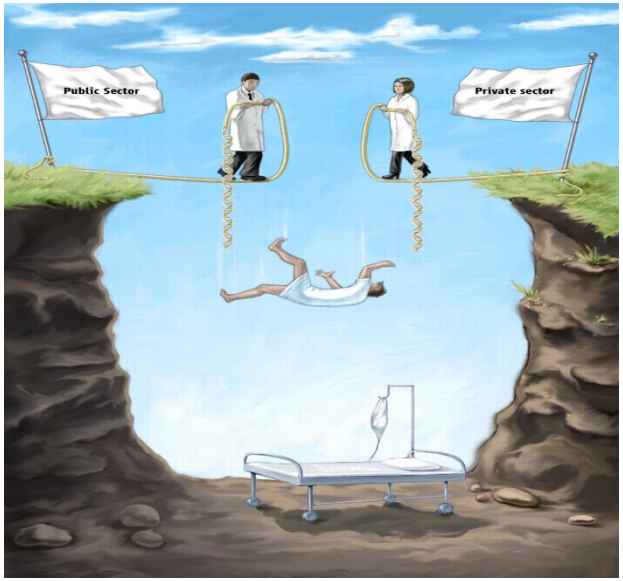
Bridging the gaps:

„Turning scientific *promise* into clinical *practice*."



„Interdisciplinarity"

Basic Scientists and researchers, regulatory experts, project managers, physicians, clinician scientists, etc. …

Mills IG and Sykes RB: Taking risks with translational research. *Sci Transl Med.* **2**, 24-10 2010

Requirements for Translational Medicine

Translation

Research → **Treatment**

Translation in University Medicine in Germany

1) Research possibility: **3.1** billion state contribution (LZB), **1.5** third p.

2) Patient access: **1.76** million in patients, **6.3** mio outpatients

3) Infrastructure: *variable* – **at MHH: CRC Hannover (ECTU)**

Translation in University Medicine

- **170.000** employees in University Medicine work in institutions with an annual turnover of **15 – 17 billion** Euro (source: German Federal Office of Statistics)
- The **education** of young academics takes exclusively place in University Medicine
- Biomedical cutting edge research is *impossible* without University Medicine (e.g. Excellence Initiative)

German University Medicine is the *perfect place* to **conduct Translational Medicine Projects**, because all necessary requirements are fulfilled !

German Science Council – recommendations infrastructure

- All **university hospitals** should continuously provide **basic infrastructure** for clinical trials (expert advise, administrative support and infrastructure).
- Establishment of comprehensive **Clinical Trial Units** as basic infrastructure
- **Permanent funding** of both ***infrastructure*** and ***specialized staff*** recommended (by german federal states or universities).
- **Reservation** of clearly defined independent spacial capacities *only* and *exclusively* for early phase proof of concept trials.

Strategiepapier für den Aufbau von Forschungsnetzwerken für klinische Studien in Deutschland. AG Infrastruktur in den Lebenswissenschaften des Forums Gesundheitsforschung, an BMBF 9.8.18

Wissenschaftsrat Empfehlungen Drs. 7301-18 ; **Hannover 19.10.2018**

Clinical Research Center (CRC) Hannover

Concept – Translational Infrastructure

Partner Alliance consists of MHH University Medicine and two Life Science research organisations:

- Hannover Medical School (MHH)
- Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM)
- Helmholtz-Center for Infectious Diseases (HZI)

Purpose:

- **Provide Infrastructure for early clinical studies (MHH and ITEM); unique QMS**
  - **Phase I:** First-in-man
  - **Phase IIa:** Proof-of-concept
- Infrastructure for National Cohort (HZI)
- **H**annover **U**nified **B**iobank HUB (MHH)

CRC Hannover at MHH

✓ Translational Alliance Lower Saxony (TRAIN)

1) **BRICS** – biology and bioinformatics
2) **Centre of Drug Research** – drug discovery
3) **TWINCORE** – preclinical research in vaccine development
4) **CiiM** - Centre for Individualised Infection Medicine
5) **CRC** – early phase clinical research – translational infrastructure

MHH

Fraunhofer ITEM

HELMHOLTZ ZENTRUM FÜR INFEKTIONSFORSCHUNG

TRAIN
Translationsallianz in Niedersachsen

CiiM
CENTRE FOR INDIVIDUALISED INFECTION MEDICINE

Clinical Research Center (CRC) Hannover

Infrastructure for Early Phase Research

- ✓ **Research Ward 1:** Phase I unit with 20 intermediate care beds (CV-monitoring)
- ✓ **Research Ward 2:** comfortable accomodation for 20 study participants as inpatients
- ✓ **Outpatient area** for physical examination, medical and social interviews and for physician – patient interaction
- ✓ **Functional area** for special diagnostic procedures (eg. ECG, Echo, lung function, endoscopy (gastro-, colonoscopy, broncoscopy, body plethysmography)
- ✓ **CRC Imaging Unit** (MRI for Clinical Research Purpose), 1.5 T MRI, 3T MRI
- ✓ **Central Biobanking** for research samples according to state of the art standards
- ✓ GMP-certified biomarker laboratory

Early Clinical Trial Unit (ECTU) at CRC

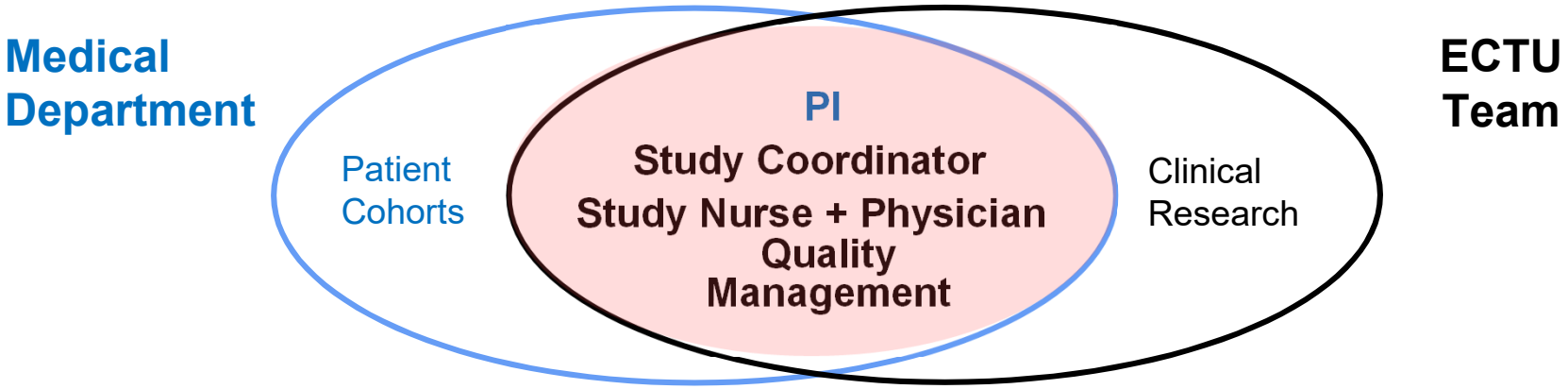
Photos: Phase I Unit – MHH Medical Team ECTU

Clinical Research Center (CRC) Hannover

Special Infrastructure Ophthalmology and ENT

Clinical Research Center (CRC) Hannover

Interdisciplinary Collaboration at MHH in the early phase

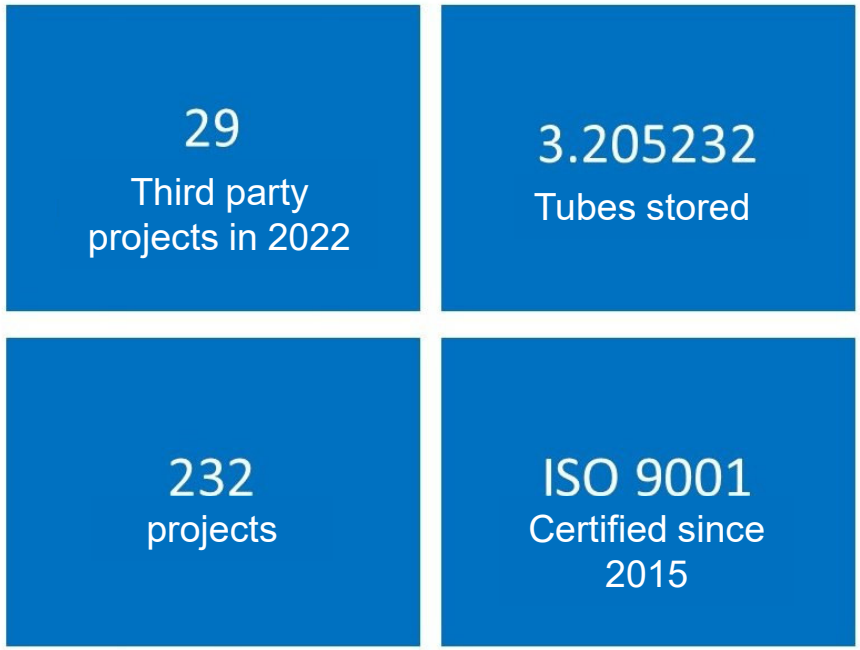


- Medical and Scientific expertise of clinical department (PI)
- Responsibility for Medicine and Science
- Expert staff (e.g. specialized nurse)
- Recruiting of specific study populations

- Clinical Trials Operation / GCP expertise / Co-PI
- Responsibility for Quality Assurance (SOP system)
- Study Conduction (e.g. PK sampling) and coordination
- Study Team (Study Nurse, documentalist), study treatment and supervision

Hannover Unified Biobank (HUB)

- Central Biobank of MHH
- Highest quality standards
- Standardized processes and automation
- Storage in nitrogen tanks at - 80 degree Celsius
- Tubes connected via Data Warehouse with clinical data



Alliance Partner

German Biobank Node
bbmri.de

HANNOVER UNIFIED BIOBANK

„Die moderne Biobank-Infrastruktur und die Professionalität, Flexibilität und hohe Effektivität des Teams der Hannover Unified Biobank ermöglichen es uns, Bioproben von gleichbleibend hoher Qualität für unsere Forschungsprojekte zu nutzen. Dies ist ein wichtiger Grundstein für unsere Erfolge in der biomedizinischen Forschung."

PD Dr. Anke Kraft
Klinik für Gastroenterologie, Hepatologie und Endokrinologie, Medizinische Hochschule Hannover

Prof. Dr. Markus Cornberg
Zentrum für Individualisierte Infektionsmedizin (CiiM), c/o Clinical Research Center Hannover

MHH – ZKS

Center for Clinical Trials

Staff Office of the CEO & President

section	section	section	section
CTS (CRO)	**OSM** (Structure)	**FRMU** (Budget, Calculation)	**ECTU** (Early Phase Unit)
Clinical Trial Services	Structure and Quality	Financial Risk Management Unit	Early Clinical Trial Unit

Research Foci at MHH

I: Infection & Immunity

II: Transplantation & Regeneration

III: Biomedical Devices & Implants

Clinical Research Center (CRC) Hannover

Collaboration with MHH Clinics and trial indications

- ✓ **Immunology and Vaccination**
- ✓ **Neurology**
- ✓ **Psychiatry (Tourette, ADHS)**
- ✓ **Ophthalmology**
- ✓ **Ear Nose and Throat (ENT)**

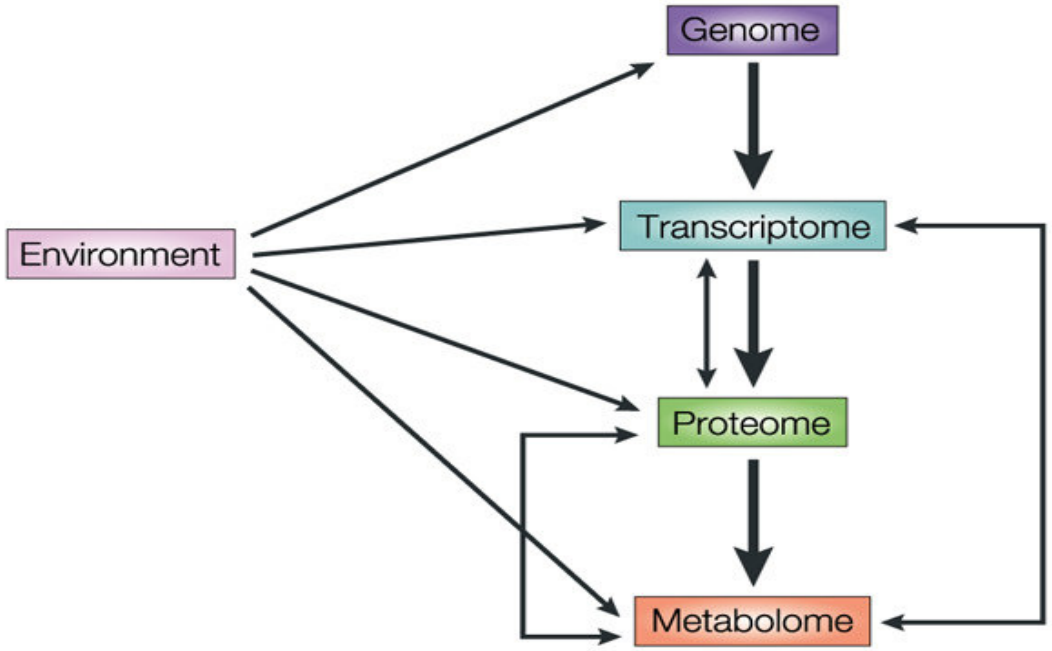
Early Clinical Trial Unit:

– Professional staff: 14

70 – 80 patient contacts/month in complex early phase trials (ECTU only)

Patient contacts 2022 (CRC in total): 6703 patient contacts, 4202 for MHH

Sucsess in translation not ex nihilo



Nature Reviews | Cancer

Strategy

People

Structures

Processes

Clin Neuroradiol
DOI 10.1007/s00062-015-0457-0

REVIEW ARTICLE

Pharmacological MRI (phMRI) of the Human Central Nervous System

H. Lanfermann · C. Schindler · J. Jordan · N. Krug · P. Raab

Drug Development

Usability of Functional MRI in Clinical Studies for Fast and Reliable Assessment of Renal Perfusion and Quantification of Hemodynamic Effects on the Kidney

The Journal of Clinical Pharmacology
2017, 00(0) 1–7

DOI: 10.1002/jcph.1034

Tobias Getzin, MD[1]*, Marcus May, MD[2]*, Martina Schmidbauer, MD[1], Marcel Gutberlet, PhD[1], Petros Martirosian, PhD[3], Reinhard Oertel, PhD[4], Frank Wacker, MD[1], Christoph Schindler, MD[2]†, and Katja Hueper, MD[1]†

Human Vaccines & Immunotherapeutics

ISSN: 2164-5515 (Print) 2164-554X (Online) Journal homepage: http://www.tandfonline.com/loi/khvi20

Establishment of a cohort for deep phenotyping of the immune response to influenza vaccination among elderly individuals recruited from the general population

Manas K. Akmatov, Peggy Riese, Marcus May, Leonhard Jentsch, Malik W. Ahmed, Damaris Werner, Anja Rösel, Megan Tyler, Kevin Pessler, Jana Prokein, Inga Bernemann, Norman Klopp, Blair Prochnow, Stephanie Trittel, Aravind Tallam, Thomas Illig, Christoph Schindler, Carlos A. Guzmán & Frank Pessler

Investigational New Drugs
https://doi.org/10.1007/s10637-018-0562-4

PHASE I STUDIES

Phase Ib study evaluating safety and clinical activity of the anti-HER3 antibody lumretuzumab combined with the anti-HER2 antibody pertuzumab and paclitaxel in HER3-positive, HER2-low metastatic breast cancer

Andreas Schneeweiss[1] · Tjoung-Won Park-Simon[2] · Joan Albanell[3] · Ulrik Lassen[4] · Javier Cortés[5,6] · Veronique Dieras[7] · Marcus May[2] · Christoph Schindler[2] · Frederik Marmé[1] · Juan Miguel Cejalvo[8] · Maria Martinez-Garcia[3] · Iria Gonzalez[3] · Jose Lopez-Martin[9] · Anja Welt[10] · Christelle Levy[11] · Florence Joly[11] · Francesca Michielin[12] · Wolfgang Jacob[13] · Céline Adessi[12] · Annie Moisan[12] · Georgina Meneses-Lorente[14] · Tomas Racek[12] · Ian James[15] · Maurizio Ceppi[13] · Max Hasmann[13] · Martin Weisser[13] · Andrés Cervantes[8]

Original Paper

Endocannabinoid Modulation Using Monoacylglycerol Lipase Inhibition in Tourette Syndrome: A Phase 1 Randomized, Placebo-Controlled Study

OPEN ACCESS

Authors
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Affiliations
1 Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Hannover, Germany
2 Abide Therapeutics, San Diego, CA, USA
3 H. Lundbeck A/S, Valby, Denmark
4 Clinical Research Center Core Facility, Hannover Medical School, Hannover, Germany.

Key words
Tourette syndrome, endocannabinoid, monoacylglycerol lipase, Lu AG06466

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accepted 12.10.2021
published online 2021

Bibliography
Pharmacopsychiatry
DOI 10.1055/a-1675-3494
ISSN 0176-3679

Supplementary Material is availabe under http://doi.org/10.1055/a-1675-3494

ABSTRACT

Introduction Tourette syndrome (TS) is a complex neurodevelopmental disorder characterized by chronic motor and vocal tics. While consistently effective treatment is lacking, evidence indicates that the modulation of endocannabinoid system is potentially beneficial. Lu AG06466 (previously ABX-1431) is a highly selective inhibitor of monoacylglycerol lipase, the primary enzyme responsible for the degradation of the endocannabinoid ligand 2-arachidonoylglycerol. This exploratory study aimed to determine the effect of Lu AG06466 versus placebo on tics and other symptoms in patients with TS.

Methods In this phase 1b cross-over study, 20 adult patients with TS on standard-of-care medications were randomized to a single fasted dose of Lu AG06466 (40 mg) or placebo in period 1, followed by the other treatment in period 2. The effects on tics, premonitory urges, and psychiatric comorbidities were evaluated using a variety of scaled approaches at different time points before and after treatment.

Results All scales showed an overall trend of tic reduction,

CNS

Pharmacopsychiatry 2022; 55 (3):
148 – 156 PMID: 34847610

BRIEF REPORT

Monoacylglycerol Lipase Inhibition in Tourette Syndrome: A 12-Week, Randomized, Controlled Study

Kirsten R. Müller-Vahl, MD,[1*] Carolin Fremer, MSc,[1] Chan Beals, MD,[2] Jelena Ivkovic, MD,[3] Henrik Loft, MSc, PhD,[3] and Christoph Schindler, MD[4]

[1]*Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Hannover, Germany* [2]*Abide Therapeutics, San Diego, California, USA* [3]*H. Lundbeck A/S, Valby, Denmark* [4]*Clinical Research Center Core Facility, Hannover Medical School, Hannover, Germany*

ABSTRACT: Background: Modulation of the endocannabinoid system via monoacylglycerol lipase inhibition with Lu AG06466 (formerly known as ABX-1431) has previously been shown to reduce tics in patients with Tourette syndrome.
Objective: The aim of this study was to evaluate the efficacy and safety of Lu AG06466 in reducing tics, premonitory urges, and comorbidities in patients with Tourette syndrome.
Methods: This was a 12-week, multicenter, randomized, placebo-controlled, double-blind clinical trial of Lu AG06466 given at two dose levels in 49 adults with Tourette syndrome.
Results: Both treatment groups showed improvement on the Total Tic Score of the Yale Global Tic Severity Scale; the mean (95% CI) treatment difference at week 8 of 3.0 (0.1, 5.9) ($P = 0.043$) favored placebo. No significant differences were seen for other endpoints assessing changes in tic severity, premonitory urges, quality of life, and common psychiatric comorbidities. Treatment with Lu-AG06466 was generally safe.
Conclusions: There was no evidence that Lu AG06466 has efficacy in suppressing tics.

Key Words: tics; Tourette syndrome; Lu AG06466; ABX-1431; endocannabinoid modulator

Tourette syndrome (TS) is a chronic, childhood-onset neurodevelopmental disorder characterized by motor and vocal tics often associated with a spectrum of psychiatric disorders. Although the neurobiological basis of TS remains unclear, most evidence supports an involvement of cortico-striato-thalamo-cortical circuits.[1] In addition to dopaminergic dysfunction,[2,3] several other neurotransmitters are likely involved, including the endocannabinoid system,[4] which, in turn, has a complex functional interaction with the dopaminergic system.[5] Hitherto, the role of the endocannabinoid system in TS has been supported by accumulating clinical evidence suggesting that cannabis-based medicines, including Δ9-tetrahydrocannabinol (THC), act as agonists at central cannabinoid CB1 receptors[6] to reduce tics and comorbid symptoms.[7-11] In addition, alterations of cerebrospinal fluid levels of the endogenous ligands (endocannabinoids) have been found.[12]

We have previously reported the results of a single-dose phase 1b study that indicated that the monoacylglycerol lipase (MAGL) inhibitor Lu AG06466 (previously known as ABX-1431) reduces tics and pre-

CNS

Mov Disord 2021 Jun 12.
doi: 10.1002/mds.28681.
Online ahead of print.

Received: 24 February 2021; **Revised:** 27 April 2021; **Accepted:** 24 May 2021

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28681

Publications Translation ZKS – ECTU 2022

- **Lancet Digital Health 2022** (MHH - IIT at CRC, CRO – Services of ZKS)
- **Nature Communications 2022** (MHH - IIT at CRC with HZI Braunschweig)
- **Clinical Infectious Diseases 2022** (Industry Research at CRC, ZKS - ECTU)

Articles

Predictive performance and clinical application of COV50, a urinary proteomic biomarker in early COVID-19 infection: a prospective multicentre cohort study

Summary

Background The SARS-CoV-2 pandemic is a worldwide challenge. The CRIT-CoV-U pilot study generated a urinary proteomic biomarker consisting of 50 peptides (COV50), which predicted death and disease progression from SARS-CoV-2. After the interim analysis presented for the German Government, here, we aimed to analyse the full dataset to consolidate the findings and propose potential clinical applications of this biomarker.

Methods CRIT-CoV-U was a prospective multicentre cohort study. In eight European countries (Austria, France, Germany, Greece, North Macedonia, Poland, Spain, and Sweden), 1012 adults with PCR-confirmed COVID-19 were followed up for death and progression along the 8-point WHO scale. Capillary electrophoresis coupled with mass spectrometry was used for urinary proteomic profiling. Statistical methods included logistic regression and receiver operating characteristic curve analysis with a comparison of the area under curve (AUC) between nested models. Hospitalisation costs were derived from the care facility corresponding with the Markov chain probability of reaching WHO scores ranging from 3 to 8 and flat-rate hospitalisation costs adjusted for the gross per capita domestic product

nature communications

Article

Distinct immunological and molecular signatures underpinning influenza vaccine responsiveness in the elderly

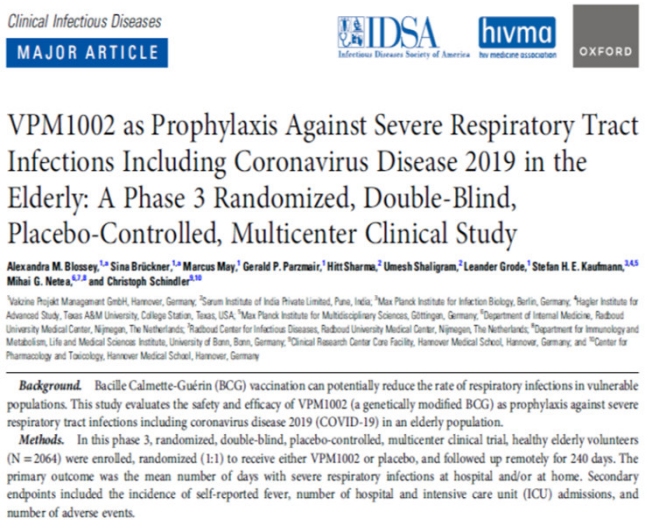
Received: 20 October 2021

Accepted: 26 October 2022

Published online: 12 November 2022

Check for updates

Seasonal influenza outbreaks, especially in high-risk groups such as the elderly, represent an important public health problem. Prevailing inadequate efficacy of seasonal vaccines is a crucial bottleneck. Understanding the immunological and molecular mechanisms underpinning differential influenza vaccine responsiveness is essential to improve vaccination strategies. Here we show comprehensive characterization of the immune response of randomly selected elderly participants (≥ 65 years), immunized with the adjuvanted influenza vaccine Fluad. In-depth analyses by serology, multi-parametric flow cytometry, multiplex and transcriptome analysis, coupled to bioinformatics and mathematical modelling, reveal distinguishing immunological and molecular features between responders and non-responders defined by vaccine-induced seroconversion. Non-responders are specifically characterized by multiple suppressive immune mechanisms. The generated comprehensive high dimensional dataset enables the identification of putative mechanisms and nodes responsible for vaccine non-responsiveness independently of confounding age-related effects, with the potential to facilitate development of tailored vaccination strategies for the elderly.



Clinical Infectious Diseases

MAJOR ARTICLE

VPM1002 as Prophylaxis Against Severe Respiratory Tract Infections Including Coronavirus Disease 2019 in the Elderly: A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Clinical Study

Background. Bacille Calmette-Guérin (BCG) vaccination can potentially reduce the rate of respiratory infections in vulnerable populations. This study evaluates the safety and efficacy of VPM1002 (a genetically modified BCG) as prophylaxis against severe respiratory tract infections including coronavirus disease 2019 (COVID-19) in an elderly population.

Methods. In this phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trial, healthy elderly volunteers (N = 2064) were enrolled, randomized (1:1) to receive either VPM1002 or placebo, and followed up remotely for 240 days. The primary outcome was the mean number of days with severe respiratory infections at hospital and/or at home. Secondary endpoints included the incidence of self-reported fever, number of hospital and intensive care unit (ICU) admissions, and number of adverse events.

Investigator Initiated Trial

Vaccination

DZIF — MHH Medizinische Hochschule Hannover — IDT

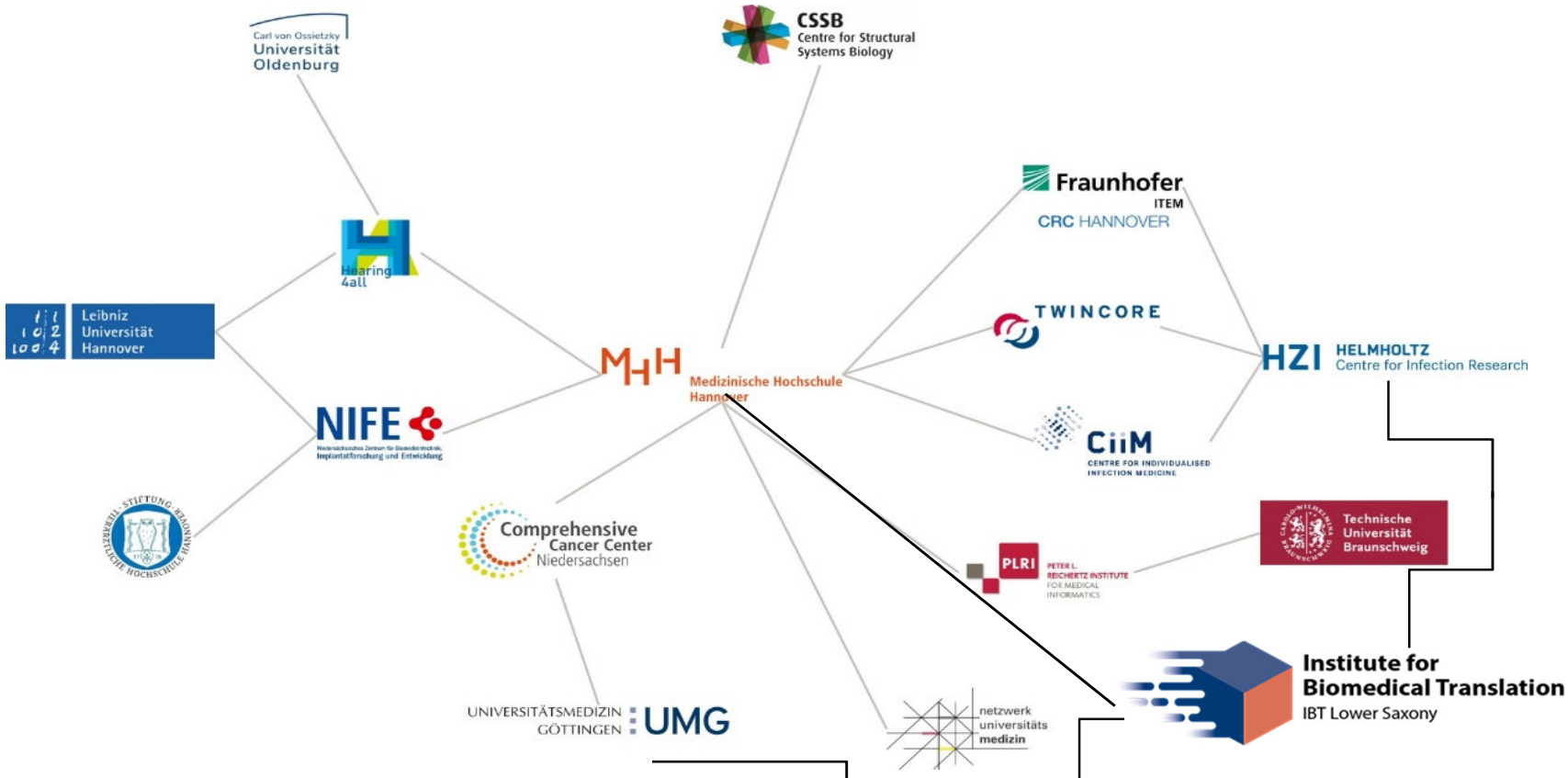
EudraCT No. 2020-004010-35 | Study Protocol | Protocol Code No. MVA-S2-S-R01

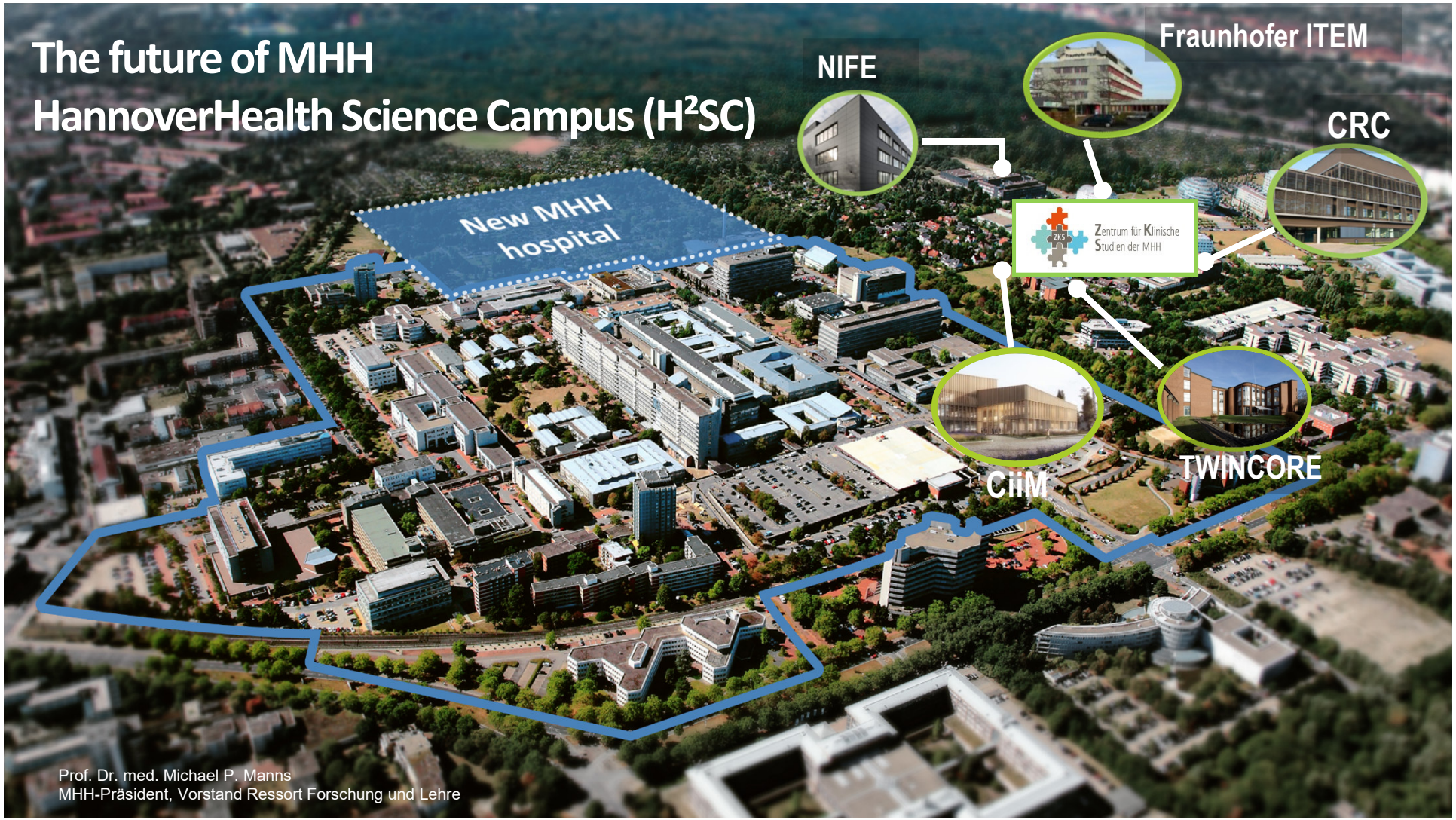
Study Protocol

Study Title:

Safety, reactogenicity and immunogenicity of a novel MVA-SARS-2-ST vaccine candidate administered as inhalation boost in SARS-CoV-2 immunized adults – phase I Study

MHH as Central Spider in Research Network of Northern Germany




The future of MHH
HannoverHealth Science Campus (H²SC)
NIFE
Fraunhofer ITEM
CRC
New MHH hospital
Zentrum für Klinische Studien der MHH
CiiM
TWINCORE
Prof. Dr. med. Michael P. Manns
MHH-Präsident, Vorstand Ressort Forschung und Lehre