NOVEL WAYS TO FIGHT PATHOGENS

Immunotherapy for Infectious Diseases

CONFERENCE 2022

June 20-23rd, 2022

UNIVERSITY OF PAVIA - ITALY

UNIVERSITÀ DI PAVIA

Technische Universität Braunschweig

Institute for Research in Biomedicine

Inserm
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From science to health

University of Pavia - AULA MAGNA
Corso Str. Nuova, 65 - 27100 Pavia PV, ITALY

www.idimmunotherapy.com
Email: conference2022@unipv.it


MARIO BARA

THE CONFERENCE

WELCOME: MONDAY JUNE 20, 2022

Monday-Thursday
June 20-23, 2022

Venue Location
Corso Str. Nuova, 65
27100 Pavia PV - ITALY
C/O AULA MAGNA,
University of Pavia

The Immunotherapy for Infectious Diseases Conference 2022
NOVEL WAYS TO FIGHT PATHOGENS

Please visit the conference website
www.idimmunotherapy.com

Organizers (in alphabetical order)

Michael Hust, Ph.D.
Professor at the Technische Universität Braunschweig - Institut für Biochemie, Biotechnologie und Bioinformatik Abteilung Biotechnologie - Braunschweig, GERMANY

Mireia Pelegrin, V.M.D., Ph.D.
CNRS Researcher - Group leader of “Antibodies & Immunomodulation” at the INSERM U1183 - Institute for Regenerative Medicine & Biotherapies (IRMB), Saint Eloi Hospital - Montpellier, FRANCE

Luca Varani, Ph.D.
Professor at the Institute for Research in Biomedicine (IRB), Universita’ della Svizzera Italiana - Bellinzona, SWITZERLAND

Livia Visai, Ph.D.
Professor at the Department of Molecular Medicine (DMM), Biochemistry Unit - UDR of ISTM and Center for Heath Technology (CHT) University of Pavia - Pavia, ITALY

01

SESSION 1
ANTIBODY-BASED DRUG DEVELOPMENT

[Moderators: Luca Varani and Harold Marcotte]

02

SESSION 2
IMMUNOTHERAPY AGAINST EMERGING VIRAL INFECTIOUS DISEASES

Part 1
[Moderators: Luca Calzolai and Andreas Laustsen]
Part 2
[Moderators: James Pettitt and Antonio Lanzavecchia]

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SESSION 3
IMMUNOTHERAPY AGAINST SARS-COV-2

[Moderators: Donata Medaglini and Leander Grode]

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SESSION 4
IMMUNOTHERAPY AGAINST BACTERIAL AND NON VIRAL INFECTIOUS DISEASES
[Moderators: Micheal Hust and Mireia Pelegrin]

05

SESSION 5
3RS PRINCIPLES IN BIOTECHNOLOGICAL AND MEDICAL APPLICATIONS

[Moderators: Livia Visai and Jonas Fuener]

CONFERENCE HOSTS

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The “Immunotherapy for Infectious Diseases Conference” brings together academia, small biotech, big pharma and regulatory bodies invested in the discovery of novel therapeutic strategies. Infectious diseases remain a leading cause of morbidity and mortality worldwide necessitating novel and innovative therapeutics. The recent COVID-19 disease caused by a SARS-CoV-2 has taught us how to react in a pandemic situation connecting scientists, researchers, medical doctors, private and public companies in order to develop and produce safe and effective vaccines as well as therapeutic antibodies in fast times.

Current and future challenges range from neglected diseases affecting the poorest countries to antimicrobial resistant pathogens in modern hospitals; from rare but deadly infections affecting few to the threat of potential global pandemics; from pathogens reaching new geographical areas due to climate changes to disease reemerging due to lack of vaccination coverage.

The ability of the human immune system to fight pathogens can be exploited for effective therapeutic strategies. Recombinant and further engineered antibodies can be used as active ingredients, as targeting agents to selectively deliver drugs or to establish novel vaccination strategies.

Bringing a novel therapy to the patients requires the combined effort of several players, all of which are brought together in the “Immunotherapy for Infectious Diseases Conference”, with world high caliber speakers and participants.

The congress is organized in the USA and Europe in alternating years with the aim to serve as a forum to exchange ideas and foster cross-disciplinary collaborations.

THE PROGRAM JUNE 20-23, 2022

The Immunotherapy for Infectious Diseases Conference

NOVEL WAYS TO FIGHT PATHOGENS

Monday June 20

12:00-2:00 PM
Registration - MAGNA HALL, University of Pavia

2:00-2:15 PM
Welcome cocktails - SALON OF THE RECTORATE, University of Pavia

2:15 PM
Welcome remarks from Prof Fausto Baldanti, University of Pavia and IRCCS Policlinico San Matteo, Pavia Italy

2:30-6:10 PM

SESSION 1

ANTIBODY-BASED DRUG DEVELOPMENT: MAGNA HALL, University of Pavia

Moderators: Luca Varani and Harold Marcotte

2:30-3:10 PM
Infectious Diseases and Antibody Therapy
KEYNOTE SPEAKER: ***Davide Corti, Humabs BioMed, a subsidiary of Vir Biotechnology, Bellinzona, Switzerland***

3:10-3:40 PM
Antibody-mediated immunomodulation: a better understanding for better antiviral immunotherapies
Mireia Pelegrin, Institute for Regenerative Medicine and Biotherapy, INSERM, Montpellier, France

3:40-4:10 PM
Recombinant snakebite antivenoms based on broadly-neutralizing oligoclonal antibodies
Andreas Hougaard Laustsen-Kiel, Technical University of Denmark, Denmark

4:10-4:30 PM Break - SALON OF THE RECTORATE, University of Pavia

4:30-5:00 PM
Public-private partnerships for development of mAbs against neglected diseases
James Pettitt, Director, Nonclinical Services, Mapp Biopharmaceutical Inc., San Diego, CA, USA

5:00-5:30 PM
Quality Assessment of Biologics and Biosimilars at Atomic Resolution
Anna Codina, Bruker Biospin

5:30-5:50 PM
Selected abstracts for 1 oral presentation

5:50-6:10 PM
Selected abstracts for 1 oral presentation

Free dinner

Tuesday June 21

8:00-8:30 AM
Registration - MAGNA HALL, University of Pavia

8:30-12:20 AM

SESSION 2 - part 1

IMMUNOTHERAPY AGAINST EMERGING VIRAL INFECTIOUS DISEASES: MAGNA HALL, University of Pavia

Moderators: Luca Calzolai and Andreas Laustsen

8:30-9:10 AM
Dissecting human antibody responses: useful, basic and surprising findings
KEYNOTE SPEAKER: ***Antonio Lanzavecchia, National Institute of Molecular Genetics, INGM, Milan, Italy And Humabs BioMed, a subsidiary of Vir Biotechnology, Bellinzona, Switzerland***

9:10-9:40 AM
Neutralizing human monoclonal antibodies against Dengue virus; towards commercialization
Pongrama Ramasoota, Mahidol University, Bangkok, Thailand

THE PROGRAM JUNE 20-23, 2022

The Immunotherapy for Infectious Diseases Conference

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9:40-10:10 AM
Fighting infectious diseases and toxins with recombinant antibodies
Michael Hust, Technische Universität Braunschweig, Braunschweig, Germany

10:10-10:30 AM
Selected abstracts for 1 oral presentation

10:30-11:00 AM **Break - SALON OF THE RECTORATE, University of Pavia - Poster section**

11:00-11:40 AM
Antibody Memory B-cell Response in Viral Infections *[on line]*
KEYNOTE SPEAKER: ***Hugo Mouquet, Institut Pasteur, Paris, France***

11:40-12:00 AM
Selected abstracts for 1 oral presentation

12:00-2:00 PM **LUNCH - SALON OF THE RECTORATE, University of Pavia**

2:00-5:30 PM

SESSION 2 - part 2

IMMUNOTHERAPY AGAINST EMERGING VIRAL INFECTIOUS DISEASES: MAGNA HALL, University of Pavia

Moderators: James Pettitt and Antonio Lanzavecchia

2:00-2:30 PM
Memory B cell response to Sars-CoV-2 Vaccines in healthy and fragile subjects
Donata Medaglini, University of Siena, Siena, Italy

2:30-3:00 PM
Controlling opportunistic viral infections in transplant recipients: antivirals and beyond
Fausto Baldanti, Policlinico San Matteo, IRCCS, and University of Pavia, Pavia, Italy

3:00-3:40 PM
Human Monoclonal Antibodies as Possible Adjuvant Treatment of Chronic Hepatitis B Virus Infection
Mario Mondelli, University of Pavia and San Matteo Hospital, Pavia, Italy

3:40-4:20 PM **Break - SALON OF THE RECTORATE, University of Pavia - Poster section**

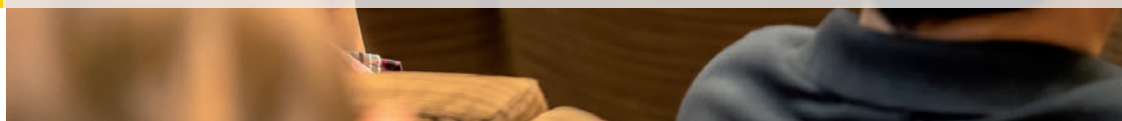
4:20-4:50 PM
Broadly neutralizing monoclonal antibodies as therapeutics for patients hospitalized with severe influenza *[on line]*
KEYNOTE SPEAKER: ***Man-Wah Tan, Genentech, USA***

4:50-5:20 PM
Antibody Therapeutics for Infectious Disease: Commercial Development Trends
[on line]
Janice Reichert, Executive Director, The Antibody Society

5:20-5:40 PM
Selected abstracts for 1 oral presentation

6:00 PM
PAVIA VISIT WITH AN ENGLISH SPEAKING GUIDE

Free dinner



THE PROGRAM JUNE 20-23, 2022

The Immunotherapy for Infectious Diseases Conference

NOVEL WAYS TO FIGHT PATHOGENS

Wednesday June 22

8:00-8:30 AM

Registration - MAGNA HALL, University of Pavia

8:30-12:30 AM

Special SESSION 3

IMMUNOTHERAPY AGAINST SARS-COV-2: MAGNA HALL, University of Pavia

Moderators: Donata Medaglini and Leander Grode

8:30-9:00 AM
Adaptive immunity to SARS-CoV-2 following infection or vaccination
Harold Marcotte, Karolinska Institutet, Stockholm, Sweden

9:00-9:30 AM
Engineering T cells to treat SARS-CoV-2 infection *[on line]*
Hugo Calderon, Hospital Clinic de Barcelona, Barcelona, Spain

9:30-10:00 AM
Immunotherapy for HIV and SARS-CoV-2 *[on line]*
Nancy Haigwood, Oregon National Primate Research Center, Oregon Health and Science University, Oregon, USA

10:00-10:30 AM
Development of COR-101 for treatment of hospitalized COVID-19 patients *[on line]*
André Frenzel, YUMAB, Germany

10:30-11:00 AM Break - SALON OF THE RECTORATE, University of Pavia - Poster section

11:00-11:30 AM
Bispecific antibodies against SARS-CoV-2
Luca Varani, IRB, Bellinzona, Switzerland

11:30-12:10 AM
The yin yang of cellular and humoral innate immunity in COVID-19
KEYNOTE SPEAKER: ***Alberto Mantovani, Istituto Clinico Humanitas, Humanitas University, Pieve Emanuele, Milano***

12:10-12:30 AM
Selected abstracts for 1 oral presentation

12:00-2:00 PM LUNCH - SALON OF THE RECTORATE, University of Pavia

2:00-5:40 PM

SESSION 4

IMMUNOTHERAPY AGAINST BACTERIAL AND NON VIRAL INFECTIOUS DISEASES: MAGNA HALL, University of Pavia

Moderators: Micheal Hust and Mireia Pelegrin

2:00-2:30 PM
Taking a closer look into the repertoire of an immune library *[on line]*
Theam Soon Lim, University Sains Malaysia (USM), Penang, Malaysia

2:30-3:00 PM
Mucosal administration of anti-bacterial antibody *[on line]*
Nathalie Heuze Vourc'h, INSERM UMR1100, Tours, France

3:00-3:30 PM
Benefiting from patient own immunity - redirecting tetanus immunity using sdAb
Jonas Fuener, Preclinics GmbH, Potsdam, Germany

3:30-3:50 PM
Selected abstracts for 1 oral presentation*y*

3:50-4:40 PM Break - SALON OF THE RECTORATE, University of Pavia - Poster section

4:40-5:10 PM
New therapeutic approaches to combat infectious diseases caused by Helicobacter pylori
Bernhard B. Singer, University Hospital Essen, Germany

5:10-5:40 PM
Prevention of Reoccurrence on TB: A new Vaccine on the Horizon
Leander Grode, VPM GmbH, Hannover, Germany

6:00 PM
VISIT TO KOSMOS MUSEUM

Free dinner

THE PROGRAM JUNE 20-23, 2022

The Immunotherapy for Infectious Diseases Conference

NOVEL WAYS TO FIGHT PATHOGENS

Thursday June 23

8:30-9:00 AM

Registration - MAGNA HALL, University of Pavia

9:00-12:15 AM

SESSION 5

3RS PRINCIPLES IN BIOTECHNOLOGICAL AND MEDICAL APPLICATIONS: MAGNA HALL, University of Pavia

Moderators: Livia Visai and Jonas Fuener

9:00-9:30 AM
Non-Animal Models in Science: Challenges & Future Direction *[on line]*
Laura Gribaldo, Scientific Officer, European Commission Joint Research Centre, Italy

9:30-10:00 AM
Replacing animals in regulated industries: Case studies in horse serum production and biocompatibility testing
Jeff Brown, Advisor, PETA Science Consortium International e.V., Germany

10:00-10:30 AM
Alternative methods and the immune system *[on line]*
Thomas Hartung, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA

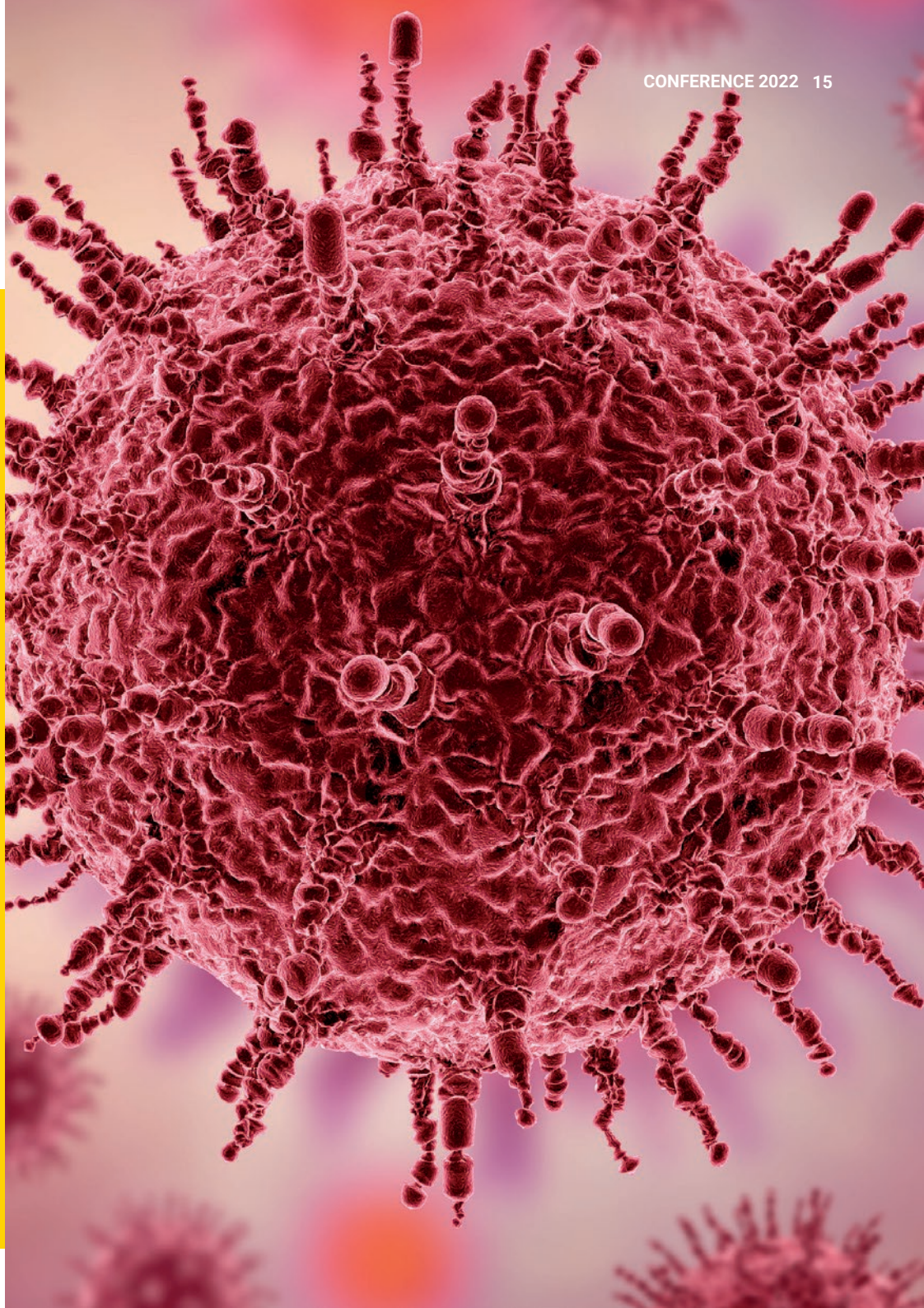
10:30-11:00 AM **Break - SALON OF THE RECTORATE, University of Pavia**

11:00-11:30 AM
How recombinant antibodies can change your scientific life *[on line]*
Pierre Cosson, University of Geneva, Geneva, Switzerland

11:30-11:50 AM
Selected abstracts for 1 oral presentation

11:50-12:00 AM
Selection of the 2 best posters

12:00-12:15 AM
CONCLUSIONS AND REMARKS



Fausto Baldanti

Full Professor, University of Pavia/Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Jeffrey Brown

Advisor, PETA Science Consortium International e.V. (PSCI)

Hugo Calderon

Hospital Clínic de Barcelona, Barcelona, Spain

Luigi Calzolai

Ph.D. - Project Leader, Joint Research Center of the European Commission

Anna Codina

Director, Pharmaceutical Business Unit, Bruker BioSpin, Bruker UK Limited

Davide Corti

Humabs BioMed, a subsidiary of Vir Biotechnology, Bellinzona, Switzerland

Pierre Cosson

Full professor at the Department of Cell Physiology and Metabolism - Faculty of Medicine, University of Geneva, Geneva, Switzerland

André Frenzel

Co-founder of YUMAB GmbH and CSO of the company, Braunschweig, Germany

Jonas Füner

General Manager of preclinics GmbH, Postdam, Germany

Laura Gribaldo

Scientific Officer- European Commission, Directorate General Joint Research Centre (JRC)

Leander Grode

Managing Director, Vakzine Projekt Management GmbH

Nancy L. Haigwood

Professor and Director, Oregon National Primate Research Center, Oregon Health & Science University

Thomas Hartung

Professor of Medical Microbiology and Immunology at Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States and Director of the Center for Alternatives to Animal Testing (CAAT)

Nathalie Heuzé-Vourc'h

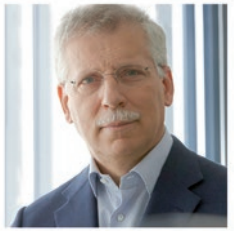
Research Director at INSERM, the National Institute of Biomedical Research, Tours, France

Michael Hust

Prof. Dr., Technische Universität Braunschweig, Institut für Biochemie, Biotechnologie und Bioinformatik, Abteilung Biotechnologie, Braunschweig, Germany

Antonio Lanzavecchia

National Institute of Molecular Genetics, INGM, Milan, Italy - Humabs BioMed, a subsidiary of Vir Biotechnology, Bellinzona, Switzerland



Andreas Hougaard Laustsen-Kiel

Center Director & Professor, Technical University of Denmark, Department of Biotechnology and Biomedicine

Lim Theam Soon

Dr. rer. nat Lecturer, Institute for Research in Molecular Medicine, Universiti Sains Malaysia

Man-Wah Tan

Vice President and Senior Fellow, Head, Infectious Diseases and Host-Microbe Interactions Genentech, A member of the Roche Group

Alberto Mantovani

Emeritus Professor at Humanitas University and Scientific Director of the Istituto Clinico Humanitas

Harold Marcotte

Associate Professor, Karolinska Institutet, Stockholm, Sweden

Donata Medaglini

PhD, Professor of Microbiology, University of Siena, Siena, Italy

Mario U Mondelli

Full professor of Infectious diseases at University of Pavia and Head of the Division of Clinical Immunology and Infectious Diseases, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Hugo Mouquet

Head of the Humoral Immunology Lab, Institute Pasteur, Paris, France

Mireia Pelegrin

Research Director at CNRS, Institute for Regenerative Medicine and Biotherapy-U1183 INSERM, Montpellier, France

James Pettitt

Director, Nonclinical Services
Mapp Biopharmaceutical Inc., San Diego CA USA

Pongrama Ramasoota

Director, Associate Professor, Center of Excellence for Antibody Research (CEAR), Head, Department of Social and Environmental Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Janice M. Reichert

PhD, Executive Director, The Antibody Society, USA.
Editor-in-Chief, mAbs

Bernard B Singer

PD Dr. rer. nat. Universitätsklinikum Essen, Institut für Anatomie, Essen, Germany

Luca Varani

PhD, Group leader, Structural Biology, Institute for Research in Biomedicine, Switzerland

Livia Visai

Associate Professor in Biochemistry at the Department of Molecular Medicine (DMM), Faculty of Medicine, University of Pavia, Pavia, Italy

POSTER TABLE

Poster presentation: Monday 20/06 - Tuesday 21/06 (to be removed at the end of the day)

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BARDELLI	VIRAL VECTORED DELIVERY OF MONOCLONAL ANTIBODY GENES AGAINST BLOOD-STAGE MALARIA	P2
BATANI	ISOLATION OF HUMAN MONOCLONAL ANTIBODIES AGAINST MULTIDRUG-RESISTANT KLEBSIELLA PNEUMONIAE	P3
BERTOGLIO	COAGULASE AS TARGET FOR IMMUNOTHERAPY AGAINST STAPHYLOCOCCUS AUREUS	P4
BURKE	A BOVINE ULTRALONG CDRH3 THAT TARGETS A CONSERVED, CRYPTIC EPITOPE ON SARS-COV AND SARS-COV-2	P5
BUTNARASU	MUCOSOMES: A NOVEL MULTI DRUG DELIVERY PLATFORM BIOINSPIRED FROM MUCIN IMMUNOMODULATORY AND ANTIMICROBIAL ACTIVITY	P6
CHORPUNKUL	DEVELOPMENT OF THERAPEUTIC ANTIBODIES AGAINST RABIES IN HUMAN USING PHAGE DISPLAY TECHNOLOGY	P7
CHRISTENSEN	PHAGE DISPLAY GUIDED DISCOVERY OF DESIGNED ANKYRIN REPEAT PROTEINS AGAINST SMALL PLANT TOXINS	P8
JENKINS	ENABLING DISCOVERY OF BROADLY-NEUTRALISING ANTIBODIES: VENOM TOXIN CLUSTERING AND UNRAVELLING SNAKE VENOM COMPLEXITY	P9
LAVENDER	NOVEL ANTIBODY–PEPTIDE CONJUGATE AGAINST MULTI-DRUG RESISTANT NEISSERIA GONORRHOEAE	P10
LOURES	DEPLETION OF MYELOID-DERIVED SUPPRESSOR CELLS MEDIATED BY THE CHEMOTHERAPEUTIC AGENT 5-FLUOROURACIL ENHANCES TH1/TH17 IMMUNITY AND CONTROL A PULMONARY FUNGAL INFECTION IN MICE	P11
MARSILE-MEDUN	DESCRIBING NEUTROPHIL IMMUNOMODULATORY PROPERTIES IN HIV-1 INFECTION AND MONOCLONAL ANTIBODY-BASED IMMUNOTHERAPY	P12
OLUDADA	THE C-TERMINUS OF PLASMODIUM FALCIPARUM CIRCUMSPOROZOITE PROTEIN IS THE TARGET OF NON-PROTECTIVE ANTIBODIES	P13

POSTER TABLE

Poster presentation: Wednesday 22/06 - Thursday 23/06 (to be removed at the end of the day)

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PERNER	ANTIBODY-MEDIATED BLUNTING OF TICK SALIVARY ENZYMATIC “CUTLERY”	P15
PITAKSAJJAKUL	POTENTIAL DENGUE THERAPEUTIC CANDIDATE THAT SHOW BOTH NEUTRALIZATION POTENCY AND ANTIBODY ENHANCING SUPPRESSION	P16
RESTIVO	CHARACTERIZATION OF ANTIBODIES SELECTED WITH PHAGE DISPLAY AGAINST STAPHYLOCOCCAL ADHESIN	P17
RIVERA DE TORRE	TINY TOXIC CRITTERS AND HOW TO BEAT THEM: DISCOVERY OF BROADLY-NEUTRALIZING HUMAN ANTIBODIES AGAINST SCORPIONS AND SPIDERS	P18
SCHUBERT	BACULOVIRUS-FREE EXPRESSION OF SARS-COV-2 PROTEINS AND VLPS IN INSECT CELLS	P19
SOOTICHOTE	PROTECTIVE EFFECT OF NS1 SPECIFIC HUMAN MONOCLONAL ANTIBODY AGAINST DENGUE VIRUS INFECTION	P20
SØRENSEN	TRENDS IN THE DISCOVERY OF CROSS-REACTIVE ANTIBODIES AGAINST SNAKE TOXINS USING ANTIBODY PHAGE DISPLAY	P21
VANZOLINI	DEVELOPMENT OF NEW BIOLOGICAL DRUGS FOR THE TREATMENT OF FUNGAL INFECTIONS	P22
WEBER	THE DROPZYLLA MICROFLUIDIC SINGLE-CELL TECHNOLOGY FOR THE MINING OF HUMAN ANTIBODY REPERTOIRES: DISCOVERY OF HIGHLY NEUTRALIZING ANTIBODIES AGAINST SARS-COV-2 AND BK-POLYOMA VIRUS	P23
WENZEL	RECOMBINANT SECONDARY ANTIBODIES TO REPLACE ANIMAL SERA	P24
YASSINE	CHARACTERIZATION OF THE IMMUNE RESPONSE IN PREVIOUSLY INFECTED MERS-COV PATIENTS AND VACCINATED WITH COVID-19 MRNA VACCINE	P25
PALLIYIL 2	MONOCLONAL HUMAN ANTIBODIES THAT RECOGNISE THE EXPOSED N AND C TERMINAL REGIONS OF THE OFTEN-OVERLOOKED SARS-COV-2 ORF3A TRANSMEMBRANE PROTEIN	P26

OLIGOCLONAL RECOMBINANT ANTIVENOM PRODUCTION THROUGH CO-CULTURE OF CHO CELLS

Anna Christina Adams [1] , Lise Marie Grav [2] , Andreas Hougaard Laustsen-Kiel [2] , Lars Keld Nielseni [1]

[1] Center for Biosustainability, Technical University of Denmark, Denmark
[2] DTU Bioengineering, Technical University of Denmark, Denmark

Email: aadams@biosustain.dtu.dk

Polyclonal antibodies continue to be used in many clinical applications including fighting infectious diseases. Snake antivenoms is an example where a mixture of antibodies is critical to neutralize a broad spectrum of toxins found in snake venom.

Synthetic anti-venoms made of multiple humanized monoclonal antibodies (mAbs) produced by individual CHO cell lines would overcome the issue of xeno-immunogenicity of conventional antivenoms (derived from horses), while enabling the design of antivenoms targeting multiple snake species.

Producing individual batches of mAbs and mixing them afterwards is associated with significant validation costs and single batch production of mAb cocktails would thus be attractive. We selected four snake toxin-specific antibodies against Sub-Saharan African snake species and generated stable anti-toxin producer clones through targeted integration in CHO cells, creating isogenic cell lines.

In this way, we aim to reduce clonal variation and the cell lines should behave similarly in a mixture. We use the same constant regions for all antibodies and the only difference in the inserted constructs is the variable regions of the antibodies (V L and V H).

The resulting cell lines were cultivated in single batches and as a mixture to compare the growth and antibody production. Growth curves revealed growth variation and significant differences in productivity across cell lines. Antibody titers ranged from 5 mg/L to 300 mg/L for different antibodies in batch culture (day five). Sequence analysis revealed recombination errors resulting in loss of the polyA-tail of the heavy chain in the lowest producer.

None of the other clones survived, which suggests that low-burden clones were selected over high-producers for this specific antibody. Further promoter engineering pointed to a need for optimization of the light/heavy chain ratio for each antibody.

Characterization of the population dynamics in the mixture is underway, as well as evaluation of engineering strategies to optimize production.

VIRAL VECTORED DELIVERY OF MONOCLONAL ANTIBODY GENES AGAINST BLOOD-STAGE MALARIA

Martino Bardelli [1,2], Amelia Lias [1], Doris Quinkert [1], Robert Ragotte [1] , Daniel Alanine [1], Thomas Rawlinson [1] , Jennifer Marshall [1] , Simon Draper [1,3]

[1] Department of Biochemistry, University of Oxford, United Kingdom
[2] Wolfson College, University of Oxford, United Kindom
[3] Jenner Institute, Nuffield Department of Medicine, University of Oxford, United Kingdom

Email: martino.bardelli@bioch.ox.ac.uk

Malaria remains one of the most devastating infectious diseases, resulting in the death of just under half a million individuals every year. Despite extensive efforts, the development of a highly efficacious and durable vaccine has proved exceedingly difficult and new and innovative intervention strategies are likely to be needed.

A significant challenge in the development of a blood-stage malaria vaccine is the need to induce, and maintain, the very high levels of antibodies necessary to neutralise the parasite's rapid invasion of red blood cells.

An alternative approach to obtain the required humoral immunity against blood-stage malaria is to use potent monoclonal antibodies (mAbs) as prophylactics, which would bypass the need for a vaccine to aid in current malaria elimination programmes.

Vectored immuno-prophylaxis (VIP) uses viral vectors such as adeno-associated virus (AAV) to deliver mAb-expressing genes, which are expressed in situ following immunisation and released into the plasma.

In this study, we deliver fully human, potently neutralising mAbs by VIP in mice, and we achieve durable and high-level serum mAb expression that is strongly inhibitory of parasite growth.

This approach, combined with anti-malarial drugs and other control interventions, could provide an effective strategy towards the ambitious objective of malaria eradication.

ISOLATION OF HUMAN MONOCLONAL ANTIBODIES AGAINST MULTIDRUG-RESISTANT KLEBSIELLA PNEUMONIAE

Giampiero Batani [1], Soraya S. Bosch [1], Vittoria Zucconi [1,2], Emanuele Roscioli [1], Dario Cardamone [1,3], Giuseppe Maccari [1], Ida Paciello [1], Chiara Mugnaini [1], Concetta De Santi [1], Giusy Tiseo [4], Cesira Giordano [4], Simona Barnini [4], Marco Falcone [4], Francesco Menichetti [4], Claudia Sala [1], Anna Kabanova [1], Rino Rappuoli [1,5]

[1] Monoclonal Antibody Discovery Lab, Fondazione Toscana Life Sciences, Siena, Italy
[2] University of Siena, Siena, Italy
[3] University of Turin, Turin, Italy
[4] University Hospital of Pisa, Italy
[5] GlaxoSmithKline Vaccines, Siena, Italy

Klebsiella pneumoniae is a major cause of healthcare-associated infections responsible for increased morbidity and mortality worldwide.

For a long time, multidrug resistance and hypervirulence were considered two non-overlapping phenotypes, as carbapenem-resistant *K. pneumoniae* (CRKP) strains are much less virulent and hypervirulent *K. pneumoniae* (hvKP) strains are usually susceptible to antibiotics. However, in recent years more and more strains have been identified integrating both phenotypes, creating multidrug-resistant strains resulting in devastating clinical outcomes.

Indeed, we are working with clinical isolates belonging to the New Delhi beta lactamase (NDM)-bearing ST147 Klebsiella from the nosocomial outbreak in Tuscany which started in 2018 and is still ongoing to date. The dramatic incidence of *K. pneumoniae* infections refractory to treatment with current broad-spectrum antibiotic classes warrants the exploration of alternative therapeutic approaches.

Our work is focused on the discovery and characterization of monoclonal antibodies (mAbs) from patients who have suffered a blood-stream infection of bla_{NDM-1}-carrying *K. pneumoniae*, with the aim to develop these mAbs as therapy and eventually find new antigens for vaccine design.

More than 200 Klebsiella-binding mAbs have been isolated from human samples and their initial characterization resulted in a shortlist including 30 highly bactericidal candidates. The IC_{50} of these mAbs in serum bactericidal assays (SBA) was ranging from 1 to 40,000 ng/mL. Moreover, some of them were cross-reactive against several genetically distant strains of *K. pneumoniae*, such as those carrying the bla_{NDM-1}, bla_{NDM-5} and bla_{NDM-9}. Additional studies are ongoing to explore the potency of the selected mAbs in cell-based assays and to identify the cognate antigens.

Taken together, these results support a promising methodology to find valuable alternatives to antibiotic treatment against bacteria that are increasingly antibiotic-resistant.

COAGULASE AS TARGET FOR IMMUNOTHERAPY AGAINST STAPHYLOCOCCUS AUREUS

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Staphylococcus aureus (SA) has been ranked by Centre for Disease Control and Prevention in the second highest tier of threats, termed serious, since antibiotic-resistant strains are widespread both in hospital-associated as well as in community-acquired infections.New antibiotic development is a long, time-demanding process and does not prevent antibiotic resistance development. Therefore, new or complementary therapies urge to be developed.

SA pathology is caused by a plethora of virulence factors able to combat multiple host defence mechanisms. Fibrinogen (Fg), a critical component in the host coagulation cascade, plays an important role in the pathogenesis of this bacterium, as it is the target of multiple staphylococcal virulence proteins. Amongst its secreted virulence factors, Coagulase (Coa) and Extracellular fibrinogen-binding protein (Efb) share common Fg binding motives and have been described to form a Fg shield around staphylococcal cells, thereby allowing efficient bacterial spreading, phagocytosis escape and evasion of host immune system responses.

Targeting these proteins with monoclonal antibodies thus represents a new therapeutic option against SA. To this end, here we report the selection and characterization of fully human, sequence-defined, monoclonal antibodies selected against the C-terminus of Coagulase. Given the functional homology between Coa and Efb, we also investigated if the generated antibodies bound the two virulence factors. Thirteen unique antibodies were isolated from HAL9/10 naïve antibodies gene libraries by antibody phage display.

As anticipated, most of the selected antibodies showed cross-recognition of these two proteins and among them, four were able to block the interaction between Coa/Efb and Fg. Furthermore, our monoclonal antibodies could interact with the two main Fg binding repeats present at the C-terminus of Coa and distinguish them, suggesting the presence of two functionally different Fg-binding epitopes.

A BOVINE ULTRALONG CDRH3 THAT TARGETS A CONSERVED, CRYPTIC EPITOPE ON SARS-COV AND SARS-COV-2

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Broadly neutralising antibodies offer huge potential as novel antibody-based therapeutics, courtesy of their ability to recognise conserved epitopes.

A sub-set of bovine antibodies possess an ultra-long complementarity determining region (CDR)H3 that is highly adept at reaching through glycan coats to recognise conserved, occluded epitopes.

Here, we use a SARS-naïve library to isolate a bovine CDRH3 that binds the receptor binding domain of SARS-CoV, SARS-CoV-2 and all SARS-CoV-2 variants. We show further that it neutralises viruses pseudo-typed with SARS-CoV Spike (IC_{50} 468 nM) but not by competition with ACE-2 binding.

Instead, using differential hydrogen-deuterium exchange mass spectrometry, we demonstrate that it recognises a rarely identified, glycan-shielded cryptic epitope that becomes available only transiently via interdomain movements of the Spike protein and where antibody binding likely triggers prefusion complex dissociation.

We therefore describe the first bovine anti-sarbecovirus paratope and illustrate a powerful approach to identify novel, potentially broadly neutralising tools to combat emerging pathogens.

MUCOSOMES: A NOVEL MULTI DRUG DELIVERY PLATFORM BIOINSPIRED FROM MUCIN IMMUNOMODULATORY AND ANTIMICROBIAL ACTIVITY

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Mucins are long polymeric glycosylated proteins composing the dense glycocalyx of mucosal epithelial cells or mucus layers covering the wet epithelia. In addition to protecting against shear stress and dehydration, mucins are also bioactive molecules towards microbes and mammalian cells.
The ever-growing emergence of antimicrobial-resistant pathogens demands innovative and transversal solutions. We aim to use the complexity of mucins in terms of structure-conferred immunomodulatory and antimicrobial activity in a novel class of mucin-based nanoparticles suitable for drug delivery, that we named “mucosomes”. The intrinsic glycosylation could allow mucosomes to engage macrophages and dendritic cells, but also bacteria and viruses through lectin-glycan interaction. The possibility of selectively targeting these cells could make mucosomes valuable drug carriers in the fight against infectious diseases. Using a one-pot synthesis method we have been able to synthesise mucosomes nanoparticles and load them with the desired drug.
A wide range of small-and macro-molecules with different physicochemical properties have been encapsulated, empowering the idea of mucosomes as a versatile drug delivery platform. Various *in vitro* models were used to test the mucoadhesive properties of mucosomes. The interaction with a glycan-binding protein (lectin) indicated the presence of functional glycans.
Mucosomes were proven to be stored at 4°C after lyophilization, and administration through a nasal spray device does not modify the morphology of the mucosomes. *In vitro* and *in vivo* tests indicated mucosomes did not induce adverse effects under the investigated conditions. By merging together, the advantages of nanomedicines with the ones of glycomimetics, mucosomes may change the paradigm of drug delivery, enabling the emerging field of mucin materials with antimicrobial and immunological activity.

DEVELOPMENT OF THERAPEUTIC ANTIBODIES AGAINST RABIES IN HUMAN USING PHAGE DISPLAY TECHNOLOGY

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Rabies has still been one of the deathly neglected neurological infectious diseases caused by rabies virus (RABV). Globally, almost 60,000 people die per year, especially in tropical area. Since neutralizing human monoclonal antibodies have been applied as therapeutic antibody for treating various viral infection in human.
In this study, the peripheral blood mononuclear cell (PBMC) of the 44 RABV-vaccinated volunteers in Thailand were collected and neutralizing antibody titer of all plasma were confirmed by RFFIT assay which range between 1.30-73.36 IU/mL. Then, the immunized human scFv libraries were constructed using pMOD1 phage display technology. All possible combinations of heavy and light chains (both kappa and lambda libraries) gene repertoires joined by a flexible serine–glycine linker were performed using a mixture of human specific primers and pull-through PCR.
We generated the $2x10^7$ and $5.4x10^6$ individual clones of VHVLκ and VHVLλ libraries, respectively. The DNA fingerprint of 32 random clones from both unselected libraries showed 29 patterns. The pooled scFv-phage clones were selected with the recombinant RABV glycoprotein and inactivated rabies virus via biopanning process for 4 rounds.
The output phage titer of the 3rd and 4th round of panning showed 10^5 – 10^6 in VHVLκ libraries and 10^3 - 10^4 CFU in VHVLλ libraries. Then, the binding specificity to RABV of the individual scFv clones were determined by ELISA assay and 10 candidate clones were suspected.
Finally, the selected scFv will be purified and tested for neutralizing activities. This research will be the initial step of the establishment of novel human anti-rabies therapeutic monoclonal antibodies in Thailand.

PHAGE DISPLAY GUIDED DISCOVERY OF DESIGNED ANKYRIN REPEAT PROTEINS AGAINST SMALL PLANT TOXINS

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Monoclonal antibodies have been developed into ‘blockbuster drugs’ and are predicted to reach a market value of 300 Billion USD in 2025. However, whilst effective, they suffer from some drawbacks that have led to a rise of new alternative binding scaffolds, such as designed ankyrin repeat proteins (DARPins).

These are substantially smaller (~15 vs ~150 kDa), which increases their potential for tissue penetration and results in cheaper manufacture at scale, when compared to immunoglobulin G antibodies (IgGs). Whilst, also containing variable regions that enable the specific and strong binding of different targets, the structure of these regions differs substantially.

Indeed, while convex in IgGs, DARPins possess concave binding regions, which could be hypothesised to be advantageous when targeting small molecules; something that has proven challenging with IgG antibodies so far and often involving complex hapten-protein conjugates.

Therefore, in this project, phage display is used to explore the potential of small molecule targeting DARPins and specifically their target binding capacity.

Notably, the success of this project would function as a proof of concept and could open possibilities for targeting so far undruggable targets using antibody-like binders.

ENABLING DISCOVERY OF BROADLY-NEUTRALISING ANTIBODIES: VENOM TOXIN CLUSTERING AND UNRAVELLING SNAKE VENOM COMPLEXITY

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Next-generation antivenoms comprised of recombinant monoclonal antitoxins are on the horizon. They carry substantial therapeutic potential for the development of safer and more effective treatment of the 2 million annual envenomations.

However, such antivenoms are challenging to develop due to the high diversity and number of toxins that require neutralisation. To enable feasible biomanufacture, it is critical to keep the number of monoclonal antibodies in a therapeutic product low. This feat is only possible if one deconvolutes venom complexity and identifies groups of similar toxins that can potentially be neutralised by the same broadly-neutralising antibody.

Therefore, in this project we clustered all currently published snake venom toxins from medically relevant toxin families using sequence-based clustering approaches. However, sequences might be insufficient predictors of cross-neutralisation potential as antibodies recognise structural, not sequence, features.

As such we also investigated structural similarity by retrieving all available toxin 3D structures, as well as computationally predicting the over 1600 structures for all remaining toxins via a bioinformatic tool developed in house.

This allowed us to identify clusters of toxins that share substantial sequence and/or structural similarity, possibly allowing for the prediction of which clusters can be neutralised by a single broadly-neutralising monoclonal antibody.

In turn, such a prediction may enable a more targeted discovery strategy that can be employed to identify a minimum set of broadly-neutralising monoclonal antibodies that can cross-neutralise one or more whole venoms.

We hope that this approach will act as a roadmap and subsequently lead to a significant acceleration of the discovery of broadly-neutralising antibodies against snake venom toxins.

NOVEL ANTIBODY–PEPTIDE CONJUGATE AGAINST MULTI-DRUG RESISTANT NEISSERIA GONORRHOEAE

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Neisseria gonorrhoeae has developed resistance to almost all conventional antibiotics.

Therefore there is an urgent need to develop novel therapies against gonorrhoea. Anti-microbial peptides have previously been investigated as novel therapies against bacterial infections but have been discontinued from further clinical testing often due to host cell toxicity.

Here we describe a novel antibody-peptide conjugate as a specific antimicrobial delivery system as a therapeutic against *N. gonorrhoeae* infection.

We generated specific monoclonal antibodies (mAbs) against an outer membrane protein of *N. gonorrhoeae*. Furthermore, we established the MIC of the antimicrobial peptides against *N. gonorrhoeae* to be in the sub-microgram/ml range against all tested strains including the antibiotic resistant WHO reference strains. Analysis of the antimicrobial activity of the antibody-peptide conjugate showed specific killing of *N. gonorrhoeae* strains which expressed the mAb target.

In conclusion, we show that anti-microbial peptides conjugated to an anti-gonococcal mAb is a efficacious, targeted, anti-microbial.

These conjugates can be further evaluated as a novel therapy to treat multi-drug resistant *N. gonorrhoeae* infections.

DEPLETION OF MYELOID-DERIVED SUPPRESSOR CELLS MEDIATED BY THE CHEMOTHERAPEUTIC AGENT 5-FLUOROURACIL ENHANCES TH1/TH17 IMMUNITY AND CONTROL A PULMONARY FUNGAL INFECTION IN MICE

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Myeloid suppressor cells (MDSCs) comprise a heterogeneous cell population characterized by myeloid origin, immature state, and suppressive activity on effector T cells in tumors and infectious diseases. However, the role of MDSCs in Paracoccidioidomycosis (PCM), the most frequent deep mycosis in Latin America, has never been investigated.

We evaluated the presence and immunosuppressive mechanisms of MDSCs in mice infected with *Paracoccidioides brasiliensis*, the etiological agent of PCM, in comparison with uninfected mice. Utilizing bone marrow-generated MDSCs, we evaluated their *in vitro* inhibitory activity on activated T lymphocytes.

To assess the function of MDSCs *in vivo*, we treated *P. brasiliensis*-infected mice with the chemotherapeutic agent 5-fluorouracil (5-FU), that specifically depletes MDSCs. A progressive increase of MDSCs in the lungs of P. brasiliensis-infected mice was observed at 72h, 2- and 8-weeks after infection, when compared with uninfected control mice. Furthermore, immunosuppressive mechanisms, such as the expression of IL-10, the enzyme IDO-1, and the checkpoint inhibitor PD-L1, were also present on MDSCs.

In vitro, MDSCs reduced the proliferation of TCD4 and TCD8 lymphocytes. Moreover, the specific depletion of MDSCs mediated by the chemotherapeutic agent 5-FU increased lung frequency of both TCD4 and TCD8 lymphocytes as well as promoted more prominent Th1 and Th17 responses, both recognized as protective in PCM. This more effective immune response resulted in regressive disease, with reduced fungal loads in target organs and decreased tissue pathology.

Furthermore, 5FU-treated mice had improved survival rates than their untreated controls. Importantly, the 5-FU treatment was innocuous to the yeasts, indicating that the improvement of the disease occurred through the modulation of MDSCs by 5-FU.

Our study demonstrated an important suppressive role of MDSCs in PCM that could be reversed by 5FU treatment, suggesting its use as new immunotherapeutic tool for PCM.

DESCRIBING NEUTROPHIL IMMUNOMODULATORY PROPERTIES IN HIV-1 INFECTION AND MONOCLONAL ANTIBODY-BASED IMMUNOTHERAPY

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The discovery of broadly neutralizing monoclonal antibodies against HIV-1 (bNAbs) has made passive immunotherapy a potential curative therapy. Besides their ability to neutralize the virus, they enhance both humoral and cellular immune response (vaccinal effect). However, the underlying cellular and molecular mechanisms involved have not yet been identified. Using a murine model of retroviral infection, we have shown that the induction of vaccinal effects by mAbs depends on the formation of immune complexes (ICs) as well as on the interaction of ICs with FcγRs expressed on multiple cells of the immune system. Among them we identified neutrophils as key cells in the enhancement of the antiviral response through their ability to activate and recruit others immune cells.

With the aim of extending these observations to the treatment of HIV infection, we investigated the immunomodulatory properties of human neutrophils in the context of bNAbs immunotherapy. We characterized the effect of (i) free HIV-1 virions, (ii) ICs made with HIV-1 and bNAbs (HIV-ICs) and (iii) proinflammatory cytokines (TNFα, IFNγ) on neutrophil functional activation as well as on the modulation of FcγRs expression.

We have shown that neutrophils secrete cytokines/chemokines involved in the recruitment/activation of other immune cells in response to these different stimuli. Furthermore, conditioning of neutrophils with proinflammatory cytokines (TNFα, IFNγ) induces a differential response to HIV versus HIV-ICs, with a 3- to 4-fold greater secretion of several cytokines/chemokines in response to ICs than to free HIV. It shows that the inflammatory environment is a determining factor for neutrophils to display a functional response to HIV/IC. Our study provides new insights into the activation of neutrophils by virus, ICs and the pro-inflammatory environment.

It may help to understand the immunomodulatory role of neutrophils during mAb treatment, which could have important implications in improving the treatment of HIV infection with bNAbs.

THE C-TERMINUS OF PLASMODIUM FALCIPARUM CIRCUMSPOROZOITE PROTEIN IS THE TARGET OF NON-PROTECTIVE ANTIBODIES

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Plasmodium falciparum (Pf) malaria, a mosquito-borne parasitic disease, remains a public health concern, especially in sub-Saharan Africa. Antibodies against the malaria vaccine target circumsporozoite protein (CSP), the major protein on the surface of sporozoites which are transmitted to humans by infected female Anopheles mosquitoes during a blood meal.

High parasite-inhibitory activity has been shown for antibodies targeting the conserved and central repeat domain, but little is known about antibodies elicited against the C-terminus (C-CSP), the immunodominant domain in recombinant CSP, that elicits much stronger humoral immune responses than the protective central repeat domain.

Here, we characterized a large panel of 48 C-CSP reactive recombinant human monoclonal antibodies (mAbs). Our data show that C-CSP reactive mAbs are frequently encoded by *IGHV3-21/IGVL3-21* gene combinations, but also by other immunoglobulin gene combinations. With one exception, which recognized a linear epitope in the C-terminal linker connecting the central repeat and C-terminal domain, all mAbs targeted the α-TSR domain, demonstrating the immunodominance of this C-CSP sub-region.

IGHV3-21 usage was strongly associated with reactivity to a conformational epitope in the α-TSR domain with high sequence diversity in Pf parasites, whereas only a few antibodies with diverse immunoglobulin genes recognized a more conserved epitope in the α-TSR domain.

However, none of the C-CSP specific antibodies bound live sporozoites or showed strong parasite inhibitory activity compared to antibodies against the repeat region. The lack of parasite reactivity and inhibitory activity was independent of mAb affinity, gene usage and epitope fine specificity. Taken together, the data suggest that the C-CSP domain on the surface of Pf sporozoites is inaccessible for antibodies and that antibodies against this domain that are elicited by immunization will not contribute to protection.

IDENTIFICATION OF NOVEL, CELL WALL PROTEIN TARGETS IN DRUG RESISTANT FUNGAL PATHOGENS AND THE SUBSEQUENT PRE-CLINICAL DEVELOPMENT OF HUMAN MONOCLONAL ANTIBODIES FOR THERAPY

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Monoclonal antibody (mAb) based therapies have seen unprecedented levels of success in cancer and autoimmune disorders, producing several blockbuster drugs. However, in infectious diseases, specifically in systemic and deep-seated fungal infections, mAbs are still in their early stages of development with currently no licensed antifungal mAbs available for patients at risk.

For these life-threatening infections clinicians must balance drug toxicity and undesirable side effects against possible treatment failure or the development of new resistant strains. As the world begins to “run out” of anti-fungal drug options, the development of next generation alternatives remains dogged by the need to kill a eukaryotic pathogen within a eukaryotic host.

Using proteomics-based approaches, we have identified several cell wall proteins (CWPs) that are over-expressed during *in vivo* infection on the surface of fungal pathogens including *Candida albicans*.

Combining techniques to identify the surface exposed regions of CWPs, and employing conventional phage display technology, we have developed a platform to generate recombinant human mAbs binding to these well-defined peptide epitopes.

These mAbs preferentially recognised *C. albicans* hyphal forms compared to yeast cells and an increased binding when the cells were grown in the presence of the antifungal agent caspofungin. In J774.1 macrophage interaction assays, mAb pre-treatment resulted in a faster engulfment of *C. albicans* suggesting a role of the CWP antibodies as opsonising agents during phagocyte recruitment.

Finally, in a series of clinically predictive, mouse models of systemic candidiasis, our lead mAb achieved an improved survival (83%) and several log reduction of fungal burden in the kidneys, similar to levels achieved for the fungicidal drug caspofungin, and superior to any anti-*Candida* mAb therapeutic efficacy reported to date.

These cell wall targeting mAbs have the potential to become a new antifungal drug class in providing alternatives to a much-limited therapeutic portfolio currently available for life-threatening fungal infections.

ANTIBODY-MEDIATED BLUNTING OF TICK SALIVARY ENZYMATIC "CUTLERY"

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Ticks salivate while feeding on their vertebrate hosts. Saliva helps tick blood-feeding through interaction and modulation of host anti-hemostatic and immunomodulatory components. Although most of the proteinaceous fraction of tick saliva is of little immunogenicity, repeated feeding of ticks on mammalian hosts leads to the formation of a few types of anti-tick antibodies and and leads to a decrease of the tick blood-feeding performance.

To identify ticks salivary antigens, we isolated immunoglobulins from rabbits that had been previously exposed to tick feeding and used the immunoglobulins for a pull-down of antigens from tick saliva. The most dominant salivary immunogens of ticks (*Ixodes ricinus*), identified in our study, were zinc-dependent metalloproteases of three different families.

To corroborate the role of metalloproteases at the tick/host interface, we fed ticks micro-injected with a zinc metalloprotease inhibitor, phosphoramidon, on a rabbit. These ticks clearly failed to initiate their blood-feeding.

However, when ticks were fed *ex vivo* on the membrane feeding system, neither feeding the "immune blood" of repeatedly infested rabbits, nor phosphoramidon injection into ticks, prevented their engorgement, clearly indicating that Zn metalloproteases play a decisive role in the success of tick *in vivo* feeding.

We argue that long (days) association of ticks with their host enables immune detection of their salivary components and that neutralisation of the identified salivary metalloproteases may facilitate an "antibody-mediated blunting of tick salivary cutlery", preventing tick infestations and possibly also the transmission of tick-borne pathogens.

POTENTIAL DENGUE THERAPEUTIC CANDIDATE THAT SHOW BOTH NEUTRALIZATION POTENCY AND ANTIBODY ENHANCING SUPPRESSION

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Dengue is one of the most important arthropod-borne viral diseases, causing both flu-like illness and severe cases, occurring mostly among patients with secondary infection with the different serotypes from the first infection, resulting from the dengue phenomenon named antibody dependent enhancement (ADE). However, no effective therapeutic drug is available to treat the disease, partly from their complexity of 4 serotypes.

So that the effective human monoclonal antibody (HuMAb) that cross-neutralization to 4 serotypes without ADE is urgent required. By using our well characterize dengue-specific HuMAb, in this study, we generated the Fc engineered HuMAb aiming to kill all 4 serotypes of dengue virus without infection enhancement. Its efficacy on neutralizing activity on Vero cell were tested.

Also, ADE activity, and serum enhancement suppression on Fc gamma receptor bearing K562 were shown. As a result, our Fc engineered HuMAb can kill all 4 serotype of dengue virus with no ADE activity.

By using dengue patient serum at dilution that showed the highest enhancing activity, our HuMAb shows complete suppression of infection enhancement. The stable cell secreting this HuMAb was also generated for further characterization for their protective activity in vivo.

In conclusion, this HuMAbs is considered as a promising dengue therapeutic candidates to neutralize virus and suppress antibody enhancement.

CHARACTERIZATION OF ANTIBODIES SELECTED WITH PHAGE DISPLAY AGAINST STAPHYLOCOCCAL ADHESIN

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Staphylococcus aureus is a human commensal bacterium; however, its pathogenic form is responsible for a great variety of infections including endocarditis and bacteremia. *S. aureus* (SA) has been treated efficiently with antibiotics until the emergence of resistance to them. Since antibiotic resistance is spreading both in clinical and non-clinical settings, there is a clear need to find new drugs to treat SA infections.

The aims of this work were to select fully human monoclonal antibodies (mAbs), through antibody-phage display, against the staphylococcal collagen-binding adhesin (CNA) and to perform a biophysical and biochemical characterization of them. Antibodies were selected against $CNA_{151-318}$ with the *in vitro* technique of antibody-phage display.

After the selection, antibody-antigen binding was characterized with Enzyme Linked Immunosorbent Assay (ELISA). We obtained 18 unique mAbs from phage display and they were characterized with ELISA assay and Surface Plasmon Resonance (SPR) technique.

The preliminary results regarding the antibody-antigen binding demonstrated that they not only bind to CNA but one of them can also recognize an adhesin expressed from another Gram-positive bacterium since they are structurally similar to CNA. In addition, the activity of the mAbs was investigated and an in-silico epitope mapping was performed through Rosetta software.

In conclusion, specific, sequence-defined, fully human monoclonal antibodies have been selected against CNA and two antibodies showed preliminary inhibiting and displacing activities. Further *in vitro* and *in vivo* studies are necessary to evaluate with accuracy their therapeutic potential.

TINY TOXIC CRITTERS AND HOW TO BEAT THEM: DISCOVERY OF BROADLY-NEUTRALIZING HUMAN ANTIBODIES AGAINST SCORPIONS AND SPIDERS

Esperanza Rivera de Torre [1], Charlotte Rimbault [1], Anna Damsbo [1], Stefanos Lampadariou [1], Shirin Ahmadi [1], Markus-Frederik Bohn [1], Andreas Hougaard Laustsen [1]

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The number of people that are medically affected by envenomings from snakes, scorpions, and spiders around the globe runs into the millions, causing life-lasting sequelae, such as amputations or even death.

Current treatments consist of antibodies derived from the plasma of immunized animals, like horses. Unfortunately, the manufacture of antivenoms against spiders and scorpions is significantly more cumbersome than similar products against snakes.

The venom amounts required for immunization are hard to obtain as the spider and scorpion “milking” processes are laborious. Indeed, venom unavailability is a significant supply chain bottleneck in antivenom production, which imposes a very high product cost, and often provokes supply shortage.

Also, plasma-derived antivenoms suffer from batch-to-batch variations, a low therapeutic content, and severe adverse immunological reactions due to the non-human nature. Therefore, it is urgent to develop alternative treatments.

This project aims to develop, for the first time, broadly-neutralizing human monoclonal antibodies against spider and scorpion toxins using phage display technology. As the medically relevant toxins are not available from the natural source, consensus toxins were designed as the “average sequence” of a collection of medically relevant toxins from brown-recluse spiders (*Loxosceles spp.*), and scorpions (*Hemiscorpius spp.*).

These were then produced and characterized, and used as antigens in a phage display selection campaign, yielding multiple cross-reactive binders.

BACULOVIRUS-FREE EXPRESSION OF SARS-COV-2 PROTEINS AND VLPS IN INSECT CELLS

Maren Schubert [1], Marcel Jaron [1], Marta Zara [2], Aidin Lak [3], Rico Ballmann [1], Philip Alexander Heine [1], Esther Veronika Wenzel [4], Federico Bertoglio [1], Silvia Stella Barbieri [2], Michael Hust [1], Stefan Dübel [1]

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The expression of recombinant proteins is an important tool in infectious diseases research – either to investigate mechanisms of the virus, for diagnostics or even as vaccine candidates.

Here, I will present the baculovirus-free expression of SARS-CoV-2 proteins like Spike in insect cells and their application. In addition, the development of SARS-CoV-2 Virus Like Particles (VLPs) and their use in cellular assays to evaluate the inhibition potential of antibodies will be described.

Such VLPs are very promising as they can resemble all molecular and morphological features of authentic virus allowing conclusive research but on the same time cannot replicate what permits handling in BSL1 laboratories.

The baculovirus-free production allows for simple adjustment of the protein ratios and has the huge advantage of a simpler purification, as no baculovirus particles contaminate the VLPs.

PROTECTIVE EFFECT OF NS1 SPECIFIC HUMAN MONOCLONAL ANTIBODY AGAINST DENGUE VIRUS INFECTION

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Dengue virus (DENV) is the mosquito-borne viral infection worldwide causing dengue fever (DF), dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS).

Interestingly, dengue virus nonstructural protein 1 (NS1) has been considered as both pathogenic agent and candidate antigen for vaccine development. Recently, not only DENV NS1 but also its antibody has elicited the cross-reactive with self-host antigens and stimulated anti-DENV NS1 antibody-mediated pathogenesis such as vascular leakage and thrombocytopenia.

To overcome the pathogenic events and reactogenicity, we generated human monoclonal antibodies against DENV NS1 from DENV-infected patients. These DENV NS1 human monoclonal antibodies (D25 and D26) were investigated the protective effects including viral neutralization and viral replication via complement pathway. Moreover, DENV-infected cells were tested cell lysis from antibody-induced complement activation.

As a result, NS1-specific human monoclonal antibodies exhibited the therapeutic effects by neutralizing all four dengue serotypes and also reduced the replication of dengue serotype 2 via complement mechanism in endothelial cell. Nevertheless, we found that human monoclonal antibodies against DENV NS1 caused complement-mediated cell lysis of infected cells.

Our findings suggest the novel potential of DENV NS1 human monoclonal antibodies as a therapeutic option against dengue disease.

TRENDS IN THE DISCOVERY OF CROSS-REACTIVE ANTIBODIES AGAINST SNAKE TOXINS USING ANTIBODY PHAGE DISPLAY

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One of the main reasons antibodies have become such a successful group of therapeutic molecules within the recent decades is that they are able to target antigens with high specificity and selectivity.

However, a different property that makes antibodies incredibly versatile is that they can be developed to be broadly-neutralizing. This property is especially relevant in areas such as infectious diseases and animal envenomings. In this project, we are investigating the use of cross-panning in phage display selection campaigns to discover cross-reactive antibodies against toxins from different snake venoms.

Snake toxins are a relevant group of antigens to work with in this regard, since the discovery of cross-reactive (and cross-neutralizing) antibodies could help to save some of the over 100,000 lives that are lost to snakebite envenoming each year. Further, snake toxins constitute a plethora of proteins that vary in size and structural similarity, from low to high homology.

These proteins can thus be used as antigens in discovery campaigns aiming to generate broadly-neutralizing antibodies, allowing for the assessment of how far cross-reactivity can be pushed via cross-panning. More specifically, we have performed cross-pannings against three phospholipases A 2 with sequence identity of ~30%, ~40%, and ~60%, two long neurotoxins with sequence identity of ~70%, and two short neurotoxins with sequence identity of ~75%. The discovered antibodies were tested in two different immunoassays and have unveiled interesting binding trends arising from the use of cross-panning.

The results from this work could help guide future discovery efforts aiming to generate broadly-neutralizing antibodies and shine light on how similar antigens must be to be useful for display campaigns utilizing cross-panning.

Finally, a few of the discovered antibodies demonstrated promising cross-reactive potential and might find utility in the development of recombinant snakebite antivenoms.

DEVELOPMENT OF NEW BIOLOGICAL DRUGS FOR THE TREATMENT OF FUNGAL INFECTIONS

Tania Vanzolini [1], Tomas Di Mambro [2], Emanuele Marra [3], Giuseppe Roscilli [3] Gianluca Morroni [4], Simona Fioriti [4], Francesco Barchiesi [4] and Mauro Magnani [1,2].

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Fungal infections are currently rising great concern especially for the rapid development and spread of resistance and the birth of new pathogenic species intrinsically multidrug-resistant.Given the limited drug arsenal and the lack of effectiveness of the available compounds, there is an urgent need for innovative approaches. Among the novel therapeutic strategies, the employment of monoclonal antibodies (mAb) is a great step forward. 2G8 is a murine mAb that selectively recognizes β-1,3 glucans, vital components of the fungal cell wall, and resulted efficient in controlling fungal infections.

Considering the immunogenicity risk due to its murine nature, we aimed in derive and characterize two humanized mAbs in different formats: a full-length mAb, Dia-T51, and a scFv, scFv-3T. Dia-T51 opsonizes C. auris cells enhancing the phagocytosis, but can also affect C. auris growth and adhesion, perturbate the fungal wall and alter the biofilm matrix alone.

On the other hand, through ELISA, SDS-PAGE and western immunoblotting, scFv-3T showed high stability and binding affinity for long time without significant aggregation tendency. Both antibodies were tested in checkerboard and time-kill curves in combination with commercially available antifungal drugs against C. auris and C. glabrata (including low susceptible strains). They demonstrated additivity with echinocandins and synergy with amphotericin B in fungal growth inhibition.

Furthermore, Dia-T51 strongly enhanced the fungicidal and the biofilm inhibitory activity of amphotericin B. In conclusion, scFv-3T and Dia-T51, both born from the murine mAb 2G8, proved comparable and sometimes better performances than their parental. They resulted effective in vitro especially in combination with other antifungals, thus suggesting that they could be new drug candidates for the treatment of fungal infections and particularly, candidiasis.

Although the encouraging results, scFv-3T must be further explored while, noted the promising preclinical outcomes of Dia-T51, we are optimistic and hopeful about its rapid moving to clinical phases.

THE DROPZYLLA MICROFLUIDIC SINGLE-CELL TECHNOLOGY FOR THE MINING OF HUMAN ANTIBODY REPERTOIRES: DISCOVERY OF HIGHLY NEUTRALIZING ANTIBODIES AGAINST SARS-COV-2 AND BK-POLYOMA VIRUS

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Sourcing antiviral antibodies directly from humans who had successfully overcome an infection has several advantages: a) the antibodies are expected to have a high probability for efficacy and safety in the clinic and b) considerable time savings can be realized during discovery and development.

MTx has developed a droplet-microfluidic single-cell-based technology platform, Dropzylla ®, that allows for the repertoire biobanking and expression of the antibodies of millions of human B cells in recombinant HEK or CHO cells while preserving the original heavy- and light chain pairing. More than 80% of the source B cells are represented in this copy and are available for a broad variety of screening methods leading to superior mAb discovery rates compared to any other technology currently available.

We have applied the technology in discovery campaigns against several viral pathogens. In our presentation we will showcase the screening processes employed and the properties of the antibodies discovered against SARS-CoV-2 and BK Virus.

With both programs superior antibodies compared to benchmarks were obtained.

The time to discovery of functionally active, neutralizing antibodies could be cut down to 21 days starting with a blood sample from a convalescent donor.

The two programs now move into clinical development and novel viral targets with high unmet medical need are currently in the discovery phase.

RECOMBINANT SECONDARY ANTIBODIES TO REPLACE ANIMAL SERA

Esther V. Wenzel [1,2], Kilian Zilkens [2] and Stefan Dübel [1]

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Recombinant antibody generation constitute the current standard for immunotherapeutics development. Beside the unique advantage of directly selecting fully human antibodies, recombinant antibodies (recAb) are anumbiguosly identified by their DNA sequence, thus they can be generated at any given time, guaranteeing illimited reproducibility. Antibody VH and VL DNA can be cloned in fusion to different moieties to produce the same antibody in different formats (e.i. scFv, Fab, IgG etc..) or with different species constant regions (human, mouse, rabbit IgG etc..).

Despite the undisputed advantages of recAbs, animal derived hybridoma and polyclonal antibodies still account for the vast majority of commercial antibody immuno-reagents for research and diagnostic. If on one side animal immunization is not anymore needed to obtain antibodies, on the other it is also causative of potentially detrimental effects for the final user.

Animal derived antibodies are characterized by a high risk of unwanted cross-reactivities and are limited in batch size, hence in their experimental reproducibility and product continuity. Yet animal derived polyclonal antibodies are the only product able to cover a broad epitope diversity and provide high sensitivity, making it highly challenging to replace them. Abcalis Multiclonals constitute a highly innovative product able to bridge the benefits of recAbs and animal derived polyclonals. Multiclonals are a defined mixture of thoroughly characterized recombinant monoclonal antibodies with different epitope specificity to the same target.

In this work, anti-human Multiclonals were compared to commercially available polyclonals and to recombinant monoclonals in a plethora of different immunoassays, including FACS, ELISA, and capillary immunoblot.

Multiclonals versatility is shown via producing Multiclonals with same antigen specificity, but different format. Finally, we show how it is possible to control at need the product target specificity (e.i. human IgG or human-rabbit IgG) by changing the individual monoclonal antibody composition of the final mixture, without any need for antigen purification. Multiclonal antibodies are the first customizable, fully reproducible, and animal-free alternative to animal derived polyclonal antibodies for research and diagnostic.

CHARACTERIZATION OF THE IMMUNE RESPONSE IN PREVIOUSLY INFECTED MERS-COV PATIENTS AND VACCINATED WITH COVID-19 MRNA VACCINE

Hadi M. Yassine [1,2], Hadeel T. Zedan [1], Maria Smatti [1], Gheyath Nasrallah [1,2], Asmaa Al Thani [1,2]

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MERS-CoV continues to circulate in camels in the Middle East and results in sporadic infections in humans. In Qatar, 30 human cases have been reported, including two recent cases in 2022. We identified a small cohort of individuals who have been infected with MERS-CoV and vaccinated with COVID-19 mRNA vaccine.

Here, we investigated the cross-reactivity of antibodies raised against MERS-CoV with other coronaviruses, including SARS-CoV-2, SARS-CoV, and seasonal coronaviruses before and after vaccination against COVID-19. We extensively characterized a total of 18 samples collected before (n=12) and after (n=6) vaccination against COVID-19. A selection of antibodies targeting significant antigens (S, N, and E) of SARS-CoV-2 and the S1 protein of SARS-CoV, MERS-CoV, and common human coronaviruses (229E, NL63, HKU1, and OC43) was analyzed using a novel antigen microarray immunoassay.

Neutralizing antibodies and antibody-dependent cellular cytotoxicity (ADCC) activity against SARS-CoV-2 were also assessed. Samples collected before vaccination showed moderate-high levels of anti-MERS IgG antibodies with some cross-reactivity against both SARS-CoV and SARS-CoV-2. However, no evidence of cross-reactivity against other coronaviruses was observed.

Samples collected post-vaccination showed significantly higher levels of total IgG antibodies targeting SARS-CoV-2 S protein, particularly IgG1. Interestingly, significant cross-reactivity with SARS-CoV was observed, specifically IgG antibodies targeting S1 protein.

Further, neutralization against both MERS-CoV and SARS-CoV-2 was higher after vaccination, suggesting possible cross-reactivity or enhanced antibody response due to the presence of shared epitopes. We identified a set of unique patients that can be used to isolate broadly neutralizing antibodies. These antibodies might help design the Pan-CoV vaccine.

MONOCLONAL HUMAN ANTIBODIES THAT RECOGNISE THE EXPOSED N AND C TERMINAL REGIONS OF THE OFTEN-OVERLOOKED SARS-COV-2 ORF3A TRANSMEMBRANE PROTEIN

Tyng Hwey Tan [1,2], Elizabeth Patton [1], Carol A. Munro [2], Dora E. Corzo-Leon [2], Andrew J. Porter [1] and Soumya Palliyil [1]

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ORF3a has been identified as a viroporin of SARS-CoV-2 and is known to be involved in various pathophysiological activities including disturbance of cellular calcium homeostasis, inflammasome activation, apoptosis induction and disruption of autophagy. ORF3a-targeting antibodies may specifically and favorably modulate these viroporin-dependent pathological activities.

However, suitable viroporin-targeting antibodies are difficult to generate because of the well-recognised technical challenge associated with isolating antibodies to complex transmembrane proteins.
Here we exploited a naive human single chain antibody phage display library, to isolate binders against carefully chosen ORF3a recombinant epitopes located towards the extracellular N terminal and cytosolic C terminal domains of the protein using peptide antigens.

These binders were subjected to further characterization using enzyme-linked immunosorbent assays and surface plasmon resonance analysis to assess their binding affinities to the target epitopes. Binding to full-length ORF3a protein was evaluated by western blot and fluorescent microscopy using ORF3a transfected cells and SARS-CoV-2 infected cells.
Co-localization analysis was also performed to evaluate the pairing potential of the selected binders as possible alternative diagnostic or prognostic biomarkers for COVID-19 infections. Both ORF3a N and C termini, epitope-specific monoclonal antibodies were identified in our study.

Whilst the linear nature of peptides might not always represent their native conformations in the context of full protein, with carefully designed selection protocols, we have been successful in isolating anti-ORF3a binders capable of recognising regions of the transmembrane protein that are exposed either on the ‘inside’ or ‘outside’ of the infected cell. Their therapeutic potential will be discussed.

june 21-22

Tuesday June 21 and Wednesday June 22, during lunch break

VISIT AT THE TERESIAN HALL OF UNIVERSITY LIBRARY

june 21

Tuesday June 21, at 18:00

Meeting point: the entrance of Magna Hall

VISIT TO PAVIA

june 22

Wednesday June 22, at 18:00

Meeting point: the entrance of Magna Hall

VISIT TO THE KOSMOS MUSEUM

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