Press Release

Institute of Molecular Biotechnology GmbH
Dr. Bohr-Gasse 3-5, 1030 Vienna, Austria
Tel: ++43-1-797 30/454
Fax: ++43-1-797 30/459
www.imba.oeaw.ac.at

July 10th, 2005

Keys to treat acute lung failure, the killer behind SARS or Avian flu

A molecular understanding of SARS regulated lung failure through ACE2 for the first time allows a rational therapy for a deadly lung disease affecting millions of people worldwide.
Findings published by Nature and Nature Medicine.

Contact:

Dr. Josef Penninger

++ 43 (1) 797 30-454
josef.penninger@imba.oeaw.ac.atl

Dr. Heidemarie Hurtl
(IMBA, IMP PR Department)
+43 1 79730-358
mobil: +43 664/8247910
hurtl@imp.univie.ac.at

Links:

IMBA Website
http://www.imba.oeaw.ac.at

„We learned to understand what makes SARS – the virus that triggered a worldwide health crisis in 2003 – such a deadly threat. Even better, SARS possibly teaches us a lesson on how to actively fight so diverse and dreadful diseases as SARS, avian flu, or the effects of biotech weapons as Anthrax", says Dr. Josef Penninger of the Vienna based Institute of Molecular Biotechnology (IMBA) of the Austrian Academy of Sciences.

In two papers that appear back-to-back in Nature and Nature Medicine, the research group lead by Josef Penninger - in particular postdoctoral fellows Yumiko Imai and Keiji Kuba in collaboration with researchers in Beijing, Toronto, and Vienna – has now found out that a key role in the infection – and in triggering the lung failure - is played by ACE2 (angiotensin converting enzyme 2), a protein well known for its role in regulating blood pressure.

Dr. Penninger and his team for the first time succeeded to genetically prove in vivo that ACE2 is a crucial SARS receptor. Their work provides a molecular explanation why and how SARS infections cause severe and often lethal lung failure. "We believe that the SARS outbreak showed us a novel medicine for a previously untreatable and often lethal lung disease that affects millions of people," emphasizes Dr. Penninger.

The significance of the work reported here extends far beyond SARS infections. SARS as well as a number of other killers have in common that they usually trigger pneumonia and acute, often lethal, lung failure. The lung gets flooded as its blood vessels leak, and it fills with body secretions. As a consequence, acute lung failure is a cause of death not only in SARS but in many other diseases such as sepsis, aspiration of gastric contents in newborns or patients in intensive care units, or patients with pancreatitis. Importantly, acute lung failure is also the principle that kills in avian flu, the famous Spanish flu in the early 20th century, or lung infections by the potential bioterrorism agent anthrax.

The current studies show that ACE2 not only has a role in SARS mediated lung failure. It protects mice just as well from severe acute lung failure induced by acid aspiration or sepsis.

Based on their new understanding on SARS infections and SARS triggered lung failure, the researchers succeeded in designing a novel and rational therapy approach. They indeed managed to effectively treat acute lung failure in mice with recombinant ACE2 and abolished the lung failure effects of SARS proteins by modulating the ACE2 pathway.

“This could provide the key for a rational therapy – that is, a cure aiming at the cause of the disease”, says Dr. Penninger, just to add: “We of course need to extend these findings in mice now to humans. Yet in essence, SARS pointed us to a protein that may help millions of people affected with a previously untreatable disease."

SARS emerged in mid-November 2002 in Guangdong Province in Southern China. With an estimated incubation period lasting less than 14 days, the coronavirus spread with surprising speed and soon infected approximately 1290 people with 55 reported deaths in Mainland China alone. Within a short while, 27 countries on 6 continents began to report illnesses.

Specific findings and implications of the current research by Dr. Penninger and his team:

During several months of 2003, a newly identified illness termed severe acute respiratory syndrome (SARS) spread rapidly from China throughout Asia to Canada and beyond, causing almost 800 deaths and disrupting travel, economics, and even scientific conventions. A novel coronavirus was identified as the SARS pathogen which triggered atypical pneumonia characterized by high fever and severe dyspnea.

The death rate following infection approached almost 10 percent due to the development of acute respiratory distress syndrome (ARDS). Moreover, influenza such as the Spanish flu and the emergence of new respiratory disease viruses have caused high lethality among infected individuals due to ARDS. The high lethality of SARS infections, its enormous economic and social impact, fears of renewed outbreaks of SARS as well as the feared misuse of such viruses as biologic weapons make it paramount to understand the disease pathogenesis of SARS and acute respiratory distress syndrome (ARDS).

ARDS is the most severe form of acute lung injury characterized by pulmonary oedema, accumulation of inflammatory cells, and severe hypoxia. ARDS affects approximately one million individuals worldwide per year and has a mortality rate of at least 30 to 50 percent. Yet, once a patient survives this acute lung failure, he or she can lead normal lives for many years.

Predisposing factors for ARDS are diverse and include sepsis, aspiration, trauma, acute pancreatitis, or pneumonias including infections with SARS coronavirus or avian and human influenza viruses. Importantly, no effective drugs exist to treat ARDS, and therapy is largely supportive with mechanical ventilation.

Based on the fact that ACE2 as a receptor is present in the lungs, the research team wondered whether ACE2 has a role in SARS pathogenesis that is acute lung failure. Subsequently, it could be shown that ACE2 protects from acute lung failure and lung oedema in models of sepsis, aspiration of acid contents and in a model of SARS-induced acute lung failure. ACE2 appears as a common injury pathway in multiple diseases that result in acute lung oedema.

ACE2, an enzyme known for its role in controlling blood pressure and even in heart failure, in this context appears in a completely new function within the renin-angiotensins system, with a novel and essential function in the lungs to control oedema and acute lung failure.

On Dr. Josef Penninger:

Josef Penninger was born in 1964 in Austria. He studied Medicine, Immunology, and History of Arts in Innsbruck. After several years of postgraduate studies at the Ontario Cancer Institute in Toronto, he worked as a lead researcher at the Amgen Research Institute in Toronto affiliated with the University of Toronto and the Ontario Cancer Institute. Since 2002, Josef Penninger is director of the newly established Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA) in Vienna. Currently, he holds the positions of Full Adjunct Professor at the Departments of Immunology and Medical Biophysics at the University of Toronto, Professor of Genetics at the University of Vienna, Austria, and Honorary Professor of the Chinese Academy of Sciences/Peking Union Medical College. The main focus of Josef Penninger's research work lies on heart and lung diseases, autoimmune diseases and cancers as well as bone diseases. His basic approach is to genetically manipulate and change genes in mice and to determine the effects of these mutations in the development of the whole organism and in diseases.
Josef Penninger received numerous prizes and honors and is the author of more than 230 papers.

IMBA

IMBA, the Institute of Molecular Biotechnology of the Austrian Academy of Sciences, combines basic and applied research in the area of biomedicine. Interdisciplinary research groups work towards understanding the fundamental molecular underpinnings of normal and pathological behavior. The ultimate aim is to translate this knowledge into novel approaches for diagnosis, prevention and therapy of diseases. IMBA is financed by the City of Vienna and the Austrian Government.

IMP- IMBA Research Center

The Research Institute of Molecular Pathology (IMP), established in 1988 by Boehringer Ingelheim, and the Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA), which went into operation in 2003, have agreed on a close research collaboration. Under the name "IMP-IMBA Research Center", the two institutes share most of the administrative and scientific infrastructure. Together, IMBA and IMP employ over 300 people from 30 different nations. Both institutes are members of the "Campus Vienna Biocenter".