

Press Release

September 15, 2006

Workshop by the Paul Martini Foundation

Molecular line of defense as target for pharmaceuticals

Bonn, September 15, 2006 (PMS). Toll-like receptors – molecules with a great significance for the immune system – are a model example of how quickly medical progress can proceed when basic researchers, industrial laboratory scientists and clinicians join forces. Not even 10 years after the discovery that mammals also have Toll-like receptors (TLRs), applications for marketing authorization may soon be filed for several TLR-stimulating pharmaceuticals. It is the objective of the workshop "Toll-like receptor-based drug development" on September 15 and 16, 2006, in Bonn to further promote this dynamic area of research in Germany. Participants were invited jointly by the University Club, Bonn, and the Paul Martini Foundation, Berlin. The event will bring together leading experts from basic research, clinics and pharmaceutical companies, including the 2004 Robert Koch Award winner, Professor Shizuo Akira from Japan. The workshop will be scientifically chaired by Professor Gunther Hartmann, University Clinic Bonn, and Professor Stefan Endres and Professor Peter C. Scriba, both from Ludwig Maximilian University, Munich.

TLRs are part of the first line of defense of the innate immune system. Immune cells such as plasmacytoid dendritic cells, which carry them membrane-bound or endosomally, can use them to recognize molecular patterns that are typical for bacteria, viruses and other pathogens and alarm other immune cells. In 1985, the *Toll* gene was discovered in flies by Christiane Nüsslein-Volhardt, who was later awarded the Nobel prize. Ever since the first mammalian TLR was identified in 1997, medical research has established that dysfunction in these receptors leads to inappropriate immune reactions during infectious diseases, cancer, sepsis and other consequences of bacterial infections.

Page 1/3

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Press Release

TLRs were quickly picked up by pharmaceutical research. A TLR-stimulating drug with the active ingredient imiquimod received marketing authorization in Germany as early as 1998 for the treatment of genital warts and basal cell carcinoma caused by papilloma viruses. However, its developers were not aware of the TLR nature of their target.

Today, on the other hand, the development of therapeutic ligands proceeds in a targeted manner with an eye on the TLR receptors to be addressed. Some projects bank on synthetic low-molecular ligands that – like imiquimod – can be used to combat viral infections. However, most TLR ligands under development are oligonucleotides that are modeled on bacterial and viral nucleic acids as the natural ligands of several TLRs.

Page 2/3

Promising applications of oligonucleotides include their use as an adjuvant in vaccines against infections. The development of so-called CpG oligonucleotides as vaccine adjuvants has reached clinical phase II. Other oligonucleotides are being tested as monotherapy for hepatitis C and other viral infections. Finally, oligonucleotides are also being tested as active ingredients for the therapy of solid tumors; a multi-center, international phase III study is currently underway for the treatment of non-small cell lung cancer. The targeted activation of certain TLRs also plays an important role in experimental tumor therapy based on vaccination with extracorporally dendritic cells that were loaded with antigens of the patient's tumor cells.

However, a TLR activation is not always the objective for oligonucleotides. It is an undesirable "side effect" for *small interfering RNAs* (siRNAs) that serve the purpose of *gene silencing*. As a result, exact knowledge regarding the structures that generate a TLR response can also serve to construct "TLR-neutral" synthetic siRNAs.

Finally, the workshop will also discuss therapeutic problems in which not the activation but the inhibition of TLR is indicated. This includes autoimmune disorders such as lupus erythematosus.

Historically as well as due to current TLR research, Bonn is excellently suited as an event venue for the symposium. After all, the foundation of oncological immunotherapy, which – as we know today – is based on TLR activation, was laid in Bonn in 1866. That same year, Wilhelm Busch, who held the chair for surgery at the Bonn University Clinic, observed that tumors temporarily recede during an infection. In 1866, even before the discovery of bacteria, he induced an infection in the tumor area of a female patient through local injury and contamination, thereby effecting a temporary regression of the tumor.

Press Release

The Paul Martini Foundation

With this workshop, the Paul Martini Foundation also celebrates the 40-year anniversary of its inception. The non-profit foundation, which is now based in Berlin, promotes drug research as well as research on pharmaceutical therapy and works to intensify the scientific dialog regarding issues of pharmaceutical therapy and development between medical scientists at universities, hospitals, the research-based pharmaceutical industry, other research institutions and government agencies. The foundation is sponsored by the German Association of Research-based Pharmaceutical Companies (VFA), Berlin, and its 40 member companies.

Page 3/3

The foundation was named after the outstanding scientist and physician from Bonn, Professor Paul Martini (1889 - 1964), in honor of his special achievements and service with regard to the advancement and continued development of clinical-therapeutic research, which he impacted significantly for decades with his "Methods of Therapeutic Examination" published in 1932. The prize awarded annually by the foundation for outstanding clinical research is also named in his honor.

This press release can be accessed at

http://www.paul-martini-stiftung.de/eng/veranstaltungen/work2006_pressemitteilung.pdf

After the event, the lecture abstracts will be available in PDF format at

www.paul-martini-stiftung.de/de/publikationen/publikationenanfordern.html