Prof. em. Dr. Dr. h.c. J. P. Kamerling
De Duiker 119
3461 JE Linschoten
The Netherlands

Letter of Recommendation to support the nomination of Dr. Vicente Verez Bencomo to the 2012 Prince of Asturias Award for Technical and Scientific Research as proposed by the Rector of the University of Havana

In the worldwide battle against infections with pathogenic bacteria, such as *Haemophilus influenzae* type b (meningitis, epiglottitis, septic arthritis, pneumonitis with empyema), *Streptococcus pneumoniae* (pneumonia, meningitis, otitis media), and *Neisseria meningitidis* (meningitis) until recently mainly capsular polysaccharide-based vaccines were in use. The capsular polysaccharide is a key virulence determinant, and antibodies directed to the polysaccharide protect humans to infections with viable bacteria.

Unfortunately, a number of disadvantages of these whole polysaccharide vaccines have remained. Capsular polysaccharides, being thymus-independent type 2 antigens, are poorly immunogenic in persons of high risk groups, such as children under the age of two, old persons, chronically ill persons, and immunocompromised patients such as splenectomized patients, transplant patients, and HIV-infected individuals.

The poor immunogenicity of the polysaccharide-based vaccines can be improved by creating a switch to a T-cell dependent response. To this end polysaccharides are conjugated with protein, preferably vaccine related proteins (toxoids), yielding so-called neoglycoconjugates. At the moment for some species, polysaccharide-protein conjugate vaccines are available. As the chemical structures of these conjugates are quite complex, being heterogeneous networks of biopolymers, straightforward analytical quality controls, as carried out for the pure polysaccharides, is impossible.

To prepare conjugate vaccines that are strongly immunogenic in persons of high risk groups, in the past it has been hypothesized that polysaccharide material can be replaced by oligosaccharide material, i.e. fragments of polysaccharides. These fragments can be prepared via degradation protocols of polysaccharides followed by isolation and via organic synthesis from monosaccharides. The big advantages of these approaches are the excellent possibilities of (analytical) quality control, not only on the oligosaccharide level, but also on the oligosaccharide-linker level, and the oligosaccharide-linker-protein level.

In 2004 the internationally first completely synthetic oligosaccharide-protein conjugate vaccine, in this case a vaccine against *Haemophilus influenzae* type b, was launched by a Cuban group of chemists and immunologists led by Dr. Vicente Verez Bencomo. The capsular polysaccharide of this pathogenic bacterium is built up from ribose-ribitol-phosphate repeating units. The final strategy was based on the organic synthesis of a suitably protected phosphate-ribose-ribitol fragment and a suitably protected spacer-phosphate-ribose-ribitol fragment. Oligomerization of these fragments led, after deprotection, to a spacered-oligosaccharide fragment of about 7 repeating units, Then, the spacered-oligosaccharide fragment was coupled via a linker molecule with thiolated tetanus toxoid, to yield the carbohydrate-protein synthetic vaccine. Although the total synthesis of the spacered-

oligosaccharide comprises several steps, the overall process could be finally accomplished under GMP conditions in high yield to a 100-gram scale per batch.
The vaccine has been evaluated in 8 clinical trials with children 4 to 5 years old in Cuba, and showed long-term, protective antibody titers that compared favourably to licenced products prepared with the *Haemophilus influenzae* type b capsular polysaccharide extracted from bacteria. The vaccine is sold under the name Quimi-Hib.

With respect to the shown possibilities in carbohydrate synthesis, the results of the Verez Bencomo group can be judged as a real breakthrough in the glycoscience community. Although carbohydrate synthesis is very complex, compared with the routinely carried out peptide and nucleotide synthesis in synthesizers (carbohydrate synthesis still needs the indispensable golden hands), Dr. Verez Bencomo and his team have shown that syntheses of carbohydrate-based drugs to high scale are really doable.

Since 2004, the activities of Dr. Verez Bencomo has found great international recognition, and has led to new interest and research activity of leading non-Cuban pharmaceutical companies, following the approach developed by the Cuban team. The present activities of Dr. Verez Bencomo, focused on the generation of new additional oligosaccharide-based vaccines for other pathogenic species, such as *Streptococcus pneumoniae* strains, are highly promising, and the glyco-community expects also for the future breakthrough results from him.

Professor Johannis P. Kamerling

Linschoten, 12 January 2012

Curriculum vitae of J.P. Kamerling

Hans Kamerling was born on 16 August 1944 in Dirksland on the island Goeree-Overflakkee in The Netherlands. After his school period (Rijks Hogere Burger School / 1957-1962), he studied chemistry at Utrecht University (UU) in the period 1962-1969 (major: Bio-Organic Chemistry; minor: Microbiology). He obtained his PhD degree at UU in 1972 with Professor Dr. J.F. Arens and Dr. J.F.G. Vliegenthart on a thesis entitled "Structure determination of oligosaccharides, an investigation of pertrimethylsilyl derivatives by mass spectrometry and PMR spectroscopy".

Connected to UU, since 1969 he has focused on the glycoscience area, in particular on the structural analysis of polysaccharides and glycoprotein glycans, on the organic/enzymatic synthesis of glycans and glycoconjugates, and on the interactions between carbohydrates and complementary biomolecules.

In 1974 he was a visiting scientist with Professor Dr. B. Lindberg at the University of Stockholm (Sweden), and in 1981 with Professor Dr. A. Kobata at the University of Kobe (Japan).

In 1990 he became University Fund Professor of Organic Chemistry of Natural Products at the Bijvoet Center for Biomolecular Research of UU, and in 2000 Full Professor of Bio-Organic Chemistry of Carbohydrates at UU. In the period 2000-2003 he acted as Dean of Studies of the Faculty of Chemistry at UU. Since 2008 he is Honorary Professor of Chemical Glycobiology at the Groningen Biomolecular Sciences and Biotechnology Institute (GBB) of the University of Groningen (RUG). Since 2009 he is Professor emeritus at UU.

In 1990 he received the Roy L. Whistler Award of the International Carbohydrate Organization for "outstanding contributions to the chemistry of carbohydrates". He is Doctor Honoris Causa of the University of Debrecen in Hungary (1999) and Profesor Invitado of the University of Havana in Cuba (2002). Since 2003, he is the Dutch representative in the European Carbohydrate Organization ECO and in the International Carbohydrate Organization ICO. Since 2007 he is secretary of the ICO. He acted also as secretary of the XIIth International Carbohydrate Symposium (1984, Utrecht, The Netherlands), the 9th European Carbohydrate Symposium (1997, Utrecht, The Netherlands), and the XVIth International Symposium on Glycoconjugates (2001, Den Haag, The Netherlands). He is vice-chair of the Executive Committee of the EuroGlycosciences Forum founded in 2008. In 2009 he was honored with the Dutch Royal Distinction "Officer in the Order of Orange-Nassau".

He was/is Editor and Board Member of several scientific journals, specifically in the carbohydrate field of research. He was Chair of the European Science Foundation (ESF) Expert Group that prepared the ESF Policy Briefing "Structural Medicine: The Importance of Glycomics for Health and Disease" (2006). He is editor-in-chief of the 4-volume Elsevier reference book "Comprehensive Glycoscience – From Chemistry to Systems Biology" (2007). He is (co-)author of over 420 scientific publications, and supervised 49 doctoral theses at UU.