Oral Session IV: Hepadnavirus Infections

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Dendrimers. Novel Antiviral Structures. G. Holan, B.R. Matthews[1], B. Korba[2], E. DeClercq, M. Witvrouw[3], E. Kern[4], R. Sidwell, D. Barnard, and J. Huffman[5] Biomolecular Research Institute, Melbourne, Australia [1]. Georgetown University, Rockville MD, USA[2]. REGA Institute, Louven, Belgium[3]. University of Alabama, Birmingham AL, USA[4]. University of Utah, Logan UT, USA[5].

Most of antiviral and other drug research, concentrates on small molecular weight structures. In contrast, we have investigated large-surface multivalent frameworks to fill peptide receptors. Synthesised were several series of dendrimers, defined as single molecular weight (monodisperse) polymeric entities, chemically built from a multifunctional core in a controlled manner. The ordered polymeric scaffold forms a three-dimensional structure that consists of concentric, or folded layers of definite structure and size. These are synthesised from previous "generation" layer functional end-groups. Each generation has an increased multiplicity of branching until for some dendrimers (e.g. polylysine) the steric crowding on the surface of the dendrimer can form a non-draining spherical shape, with a known number of reactive functional groups. These groups on the outer surface of the dendrimer are then capped with functionalised chemical moieties that are recognised by a biological receptor. Some of the sterically hindered dendrimers are not recognised by degradative enzymes and do not act as antigens. The dendrimers have polyvalent attachment into receptors and their size, substitution, volume, nature and number active groups can be controlled. The surface of several dendrimers cores e.g. polyamidoamines (PAMAM), polylysines and novel poly-gallates were functionalised with selected surface groups. Unlike in other biological uses for dendrimers, as polymeric carriers for drugs, antigens etc., the whole dendrimers are used as drugs in their own right, controlled by the properties of the surface groups. We have found that many aryl anionic surface groups form dendrimer structures with high antiviral activities. The surface of the antivirally active dendrimers can be modified, to control biological properties. Testing has demonstrated high, sometime selective activities against HIV, HBV, CMV, HSV-1 and HSV-2, and the respiratory complex of RSV and Flu viruses. The antiviral activity, cell and tissue penetration and other biological investigations will be presented.

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Anti-hepatitis B specific β-L-2'-deoxynucleosides. ML Bryant[1], G Gosselin[2], RF Schinazi[3], and J-L Imbach[2], and J-P Sommadossi[4]. [1]Novirio Pharmaceuticals; USA; [2]Univ. de Montpellier II, France [3]Emory Univ. and VA Med. Center, Decatur, GA, USA; [4]University of Alabama at Birmingham, USA.

Current treatment of chronic hepatitis B virus (HBV) infection is suboptimal due to drug-related toxicity, low response rates, unsustained viral load reduction, and rapid emergence of antiviral drug-resistance. More potent, selective and specific antiviral drugs are needed to maximally and durably suppress chronic HBV replication. β-L-2'-Deoxynucleosides with potent anti-HBV specific activity have now been discovered. This series of compounds has in common the presence of a 3'-hydroxyl group that renders the compounds inactive against other viruses and specifically active to varying degrees against hepadnaviruses. β-L-Thymidine (L-dT, NV-02B) and β-L-2'-deoxycytidine (L-dC, NV-02C) were the most potent inhibitors of the series against HBV, WHV, and DHBV replication, but did not inhibit HIV, RSV, HSV, VZV, HCMV, EBV, measles virus, adenovirus, rhinovirus, influenza and parainfluenza virus replication. Both compounds lacked cytotoxicity in animal and human primary cells including bone marrow progenitor cells, exhibited no mitochondrial toxicity or incorporation into mitochondrial or cellular DNA, did not inhibit human cellular DNA polymerases and were non-mutagenic. L-dT and L-dC were activated to their respective 5'-triphosphate forms by cellular kinases including dCK and TK1 or TK2. In a woodchuck chronic hepatitis model, viral load reduction was dose dependent and at 10 mg/kg/d given orally L-dT and L-dC were safe and reduced plasma virus load by up to 8 logs as defined by quantitative PCR. The *in vitro* and *in vivo* pharmacokinetic profile and the sustained antiviral activity after drug-withdrawal suggest that once-a-day oral dosing is possible. The unique profile of these potent and specific anti-hepatitis B drug candidates warrants their rapid clinical development.