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Peptoids: An Emerging Class of Peptidomimetics for Cancer Therapy and Diagnostics

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Abstract

Conventional methods used to treat cancer, from non-specific chemotherapy to modern molecularly targeted drugs have generated limited results due to the complexity of the disease as well as lack of molecular classes that can be developed into treatments rapidly, easily and economically. Peptoids are class of peptidomimetics that are easy to synthesize and optimize and has been studied in different oncology applications as great biologically amenable compounds and can be considered as a promising alternative molecular class for anticancer drug developments.

Keywords: Peptoids; Drug development; Cancer

Introduction

A perfect drug that is effective on the majority of the cancer types, or at least a majority of patients within a single cancer type, has yet to be discovered. Conventional chemotherapies used to treat cancer generated limited results mainly due to high level of side effects. The emergence of targeted drug developments signifies a paradigm shift in cancer therapy development arena. Although the diversity of targets giving rise to this new generation of anticancer drugs has expanded,many challenges persist in the design of effective treatments.One of the reasons for this is the paucity of perfect 'drug-like' molecular classes that can be developed from bench to bedside rapidly, effectively and economically. The statistics of developing one drug out of 10,000 compounds studied over 10-15 years with spending $1-2 billion, has not been changed to date and therefore alternate molecular classes are needed to be explored to make this whole drug development process more efficient and economical.

The well-known molecular classes in the modern drug development arena, such as small organic molecules, antibodies, peptides and nanoparticles, carry both useful as well as undesired properties [1]. Years ago, small organic molecules exclusivelyrepresented therapeutics aseasy to handle and orally available chemical compounds. However, the synthesis of majority of biologically active complex organic compounds remains a challenge to date.In addition,these molecules clear through the kidneys and do not have adequate affinity and contact time for effective imaging or therapy of the tumor. During the last decade or so, antibodies have been developed as high affinity and specificity drugs, but this is a costly approach and also antibodies have intermediate to poor bio-distribution and tumor penetration. Other traditional macromolecules, such as nanoparticles, virtually have no clearance from the bodywhichraisesfundamental questions on their use as drugs.In the meantime, peptides as intermediate size moleculesemerged as great therapeutics, but current development of peptide-based pharmaceuticals is hindered by their rapid *in vivo* degradation. Researchers have recently investigated alternative peptide-like constructs that may be able to circumvent such complications.This is the point where peptidomimetics or peptide-like molecular developments were initiated, and peptoids are emerged as one such a promising molecular class, in particular in oncology applications.

Peptoidswere originally invented in the early 1990s by Prof. RonaldZukermann and majorbiological applications were begunwithin the last decade, primarily spearheaded by Prof. Thomas Kodadek's group[2,3].Peptoids comprise a peptide-based backbone and N-substituted glycines(Figure 1). This means the side chain ('R' group) is placed on the nitrogen atom of the amide bond in peptoids as compared to the alpha-carbon in peptides, bringing unique and favorable characters over peptides and other conventional drug classes.The solid-phase (on resin beads) submonomerpeptoid synthesis isvery efficient, rapid, economicaland straightforward (Figure 2) [4]. In order to add one residue (equivalent to an amino acid of a peptide), it needs only two chemical stepsand each of these steps can be completed by 2 x 15 second microwave pulses (Figure 2) [5].Bromoacetic acid coupling brings the two carbon units and the Br can be replaced by *any amine* group, which dramatically expands the repertoire of chemical space. In peptides there are only 20 side chains available

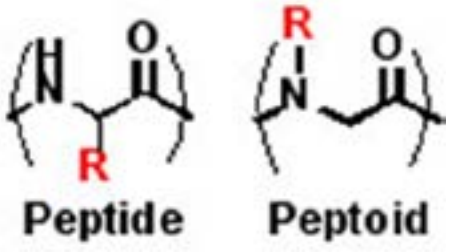

Figure 1: Peptide vspeptoid.

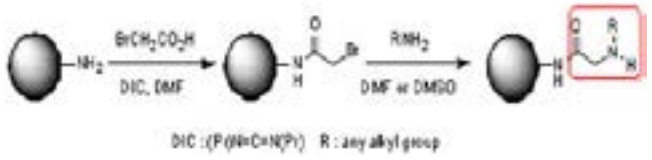

Figure 2: Peptoid synthesis out line.

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through natural amnio acids, but in peptoids, virtually any organic moiety ('R' groups) can be incorporated into the back bone,thereby tremendously increasing the target bio-molecular recognition capacity. These oligomers are protease resistant, more cell permeable, non-immunogenic, achiral and adopt different conformations than peptides, yet retain the same density of functionality and backbone polarity[3,6,7]. Synthesis of peptoid sequences up to about 50 units in length allows for controlled sequence composition and incorporation of diverse side chain chemistries. It became clear very quickly that the most significant hurdle to compete in the drug discovery race was to access to large collections of compounds forhigh throughput screens. Large combinatorial libraries of peptoids (in millions) can be synthesized easily, inexpensively, and rapidly (less than one week)[8-12]. Peptoid sequences can be deduced sensitively by Edman degradation[9,10] or mass spectrometry[11-13].

The anti-cancerpeptoid drug-lead discovery is mainly relying onhigh throughput screenings of large peptoidcombinatorial libraries. These peptoid libraries are synthesized through the "split-pool" approach, and these split-pool cycles will lead to development of 'one-bead one-compound' (OBOC) libraries with huge diversity[14,15].For example, the Kodadek group developedseveral number of suchpeptoid librarieswith diversities varied up to millions of permutations[3,9,12,16-18]. These peptoid libraries are developed in less than one week, using the very efficient and rapid microwave synthesis method. All other molecular classes are needed much more time and effort in order to develop similar size libraries and peptoids clearly display huge advantage in this initial development levels.

Once developed, these OBOC libraries can be utilized in two major types of screens, namely (I) protein, and (II) cell screens to rapidly identify specific peptoids for our favorite biological target (bio-marker) that is important in oncology applications. In protein screens,the interested protein is equilibrated with OBOC library beads and the proteinis allowed to 'pick' the best binding sequences. Those protein-binding peptoid carrying beads ('hits') are identified via having a fluorascein tag (e.g. GFP) on the protein or by employing a secondary identification system (e.g. GST- or Fc-recognizing fluorescein/ quantum dotlabeled antibodies). The peptoid sequence on that 'hit' bead is subsequently identified via Edman degradation or mass spectrometry. For example, Kodadekgroup reported severalpeptoidsthat were identified through these protein screens targeting;the human Mdm2 protein (a negative regulator of p53 function and a potential anti-cancer drug target),[9]the mammalian coactivator CREB-binding protein (CBP)[16] andthe proteasome 19S regulatory component[12].

Asa second and improved screening approach, a unique cell based technology was developed to identify the most specific peptoids 'directly' from the initial screen[10,19]. The screen is based on the capability of the library compounds to recognize the 'target bio-marker [e.g., VEGF-receptor-2(VEGFR2)] expressing' cell group (red stained) over a 'target non-expressing' cell group (green stained), through binding to that target bio-marker. By applying this methodology over the last few years, we were able to successfully identify and validate high affinity and specific peptoid ligands for VEGFR2 (found in endothelial cells in tumor blood vessels[10],Fibulin-5 (a novel protein important in angiogenesis),lung cancer cell lines[20]and cancer stem cells. The VEGFR2 targeting peptoid inhibited new blood vessel formation (angiogenesis) towards the tumor and hence reduce the tumor growth in mice [10,21,22].In addition, there are several other reports describe the use of peptoid based applications in cancer as well[23-28].

As an effort to develop better cancer diagnostic tools, we attached an imaging agent [(Gd(III)-DOTA)8 dendron] to the VEGFR2 binding peptoid and the imaging agent was specifically delivered to the MDA-MD-231 breast tumors in mice[29]. The tumor was clearly 'lit up' in the Magnetic Resonance Imaging (MRI) study. This was one of the first demonstrations of the use of MRIfor nanomolar level targeted imaging of bio-markers (MRI is less sensitive otherwise). In another study, ^{64}Cu-labeled DOTA conjugates of this same peptoid was used to image PC3 prostate cancer cells using small animal Positron Emission Tomography (PET)[30].

In comparison to peptides, reported data indicated that peptoids have higher tissue accumulation, moderateexcretion, and higher *in vivo* stability. Remarkably longer passage through the gastrointestinal (GI) tract without rapid digestion was observed for peptoids confirming the great *in vivo* stability. As already mentioned, peptoid synthesis and further optimizations are extremely versatile and economical to handle. As protease-resistant isomers of peptides, peptoids are being developed as useful molecular tools in biochemistry and biophysics, and are becoming attractive candidates for therapeutic, diagnostic and many other applications in cancer.Peptoids have thus far demonstrated very promising bioactivitiesin oncology and also various other disease areas as peptide mimics and can be considered as better alternativefor small molecular, antibody and peptide drugs in the future.

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