Groups 4 and 15 and Organotin Condensation Polymers for The Treatment of Cancers and Viruses

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Abstract

This short review describes the use of group 4 metallocenes, group 15 organometallics and organotin polymers in the treatment of human cancer tumors and viruses. These metal-containing polymers show good inhibition of all the main group solid tumors including pancreatic, lung, brain, breast, prostate and colon human cell lines. They also show inhibition of a variety of viruses including zika, herpes and vaccinia viruses. Synthesis of the polymers is rapid employing interfacial polymerization and commercially available reactants. They offer physicians a new class of drugs for the treatment of a variety of cancers and viruses.

Keywords: Cancer; Viruses; Interfacial polymerization; Brain cancer; Pancreatic cancer; Zika virus; Vaccinia virus; Breast cancer; Herpes virus

Introduction

Use of metal-containing agents to treat various medical problems is well known [1-22]. Here the focus is on activities to supply metal-containing polymers for the treatment of various cancers and viruses. While we have had extensive experience with platinum and palladium polymers for the treatment of a variety of cancers, the current emphasis is on polymers formed by incorporation of groups 4 and 15 metals and organotin condensation polymers for the treatment of cancers and viruses [23-41]. These two polymer types are different with their own separate biological characterizations [26]. For instance, the platinum and palladium polymers are addition products and not stable for long times in solution. By comparison, the groups 4 metallocene and organotin and group 15 polymers are condensation polymers and exhibit good stability to over 30 weeks in solution so can be treated differently with respect to biological and physical characterizations [26-41].

Synthesis

Synthesis occurs employing interfacial polymerization [42-46]. It is a rapid polymerization system because high-energy reactants are employed. These high-energy reactants are acid halides. A typical condensation reaction has an activation energy of about 30-40Kcal/mol whereas the activation energy for the acid halide reactions is on the order of 20Kcal/mol. The interfacial polymerization is employed industrially to synthesize aromatic polyamides (nylons) and polycarbonates so industry is familiar with the system [47,48]. These interfacial polycondensation reactions form polymer within less than one minute in decent yield. For the syntheses described here, commercially available reactants are employed allowing ready reproduction and scale-up to ton levels in a somewhat straightforward manner. Rapid stirring is employed, generally about 18,000 rpm. This allows both the rapid
polymerizations to occur with an increase in interfacial contact area of over ten thousand compared to non-stirred systems, and good reproducibility. For the systems described here, the reaction vessel is a simple glass reaction vessel, one-quart Kimax emulsifying jar, fitted onto a Waring Blender. To illustrate the overall reactions, products formed for the organotin polymers have a repeat unit described as follows.

\[ R_2SnX_2 + X-R-Y \rightarrow (-SnR_2-R)- \]

where X and Y are normally Lewis bases such as alcohols, amines, acid salts, thiols, etc. These reaction sites are often varied for a single Lewis base such as an amino acid, shown below, that has both acid and amine reactant sites. Examples of overall reaction products for each of the three condensation polymer groups are given following. Reaction between the amino acid diglycine and dimethyltin dichloride is described (Figure 1). The polymer is described as a poly (amine ester) with the organotin unit considered an organic moiety such as a methylene unit in such naming. For the Group 4 metallocenes, the reaction employing titanocene dichloride as the Lewis acid, the repeat unit for a product formed from titanocene dichloride and chelidonic acid is given (Figure 2). Finally, for reactions involving group 15 metals, the repeat unit formed from reaction between triphenylantimony dichloride and 3,5-pyridinedicarboxylic acid forming a polyester is given (Figure 3). The metal is generally located in the Lewis acid portion while the non-metal reactant is the Lewis base. In certain cases, the Lewis base portion may also contain a metal, usually iron and cobalt. The iron is present as a ferrocene while the cobalt is present as a cobaltocene [32].

![Figure 1: Synthesis of organotin poly (amine esters) from reaction of diglycine and dimethyltin dichloride where R represents simple chain extension.](image1)

![Figure 2: Synthesis of polyesters from reaction with titanocene dichloride and chelidonic acid where R represents simple chain extension.](image2)

Cancer

It was initially mistakenly assumed that these metal-containing compounds inhibited cancer by the same mechanism as the platinum-containing drugs as cisplatin and other similar platinum containing drugs [26,50]. (The platinum-containing drugs currently are employed in over 60% of the chemo drug treatments generally as one of the components.) It is now known that this is not true so that they can be coupled with the drugs described here as co-drugs that will affect inhibition of cancer through two distinct avenues. The platinum-containing drugs are quite toxic resulting in the presence of many negative side effects [26]. Our effort is to create drugs that have similar or superior ability to inhibit cancer but without the unwanted side effects. All of the metal-containing drugs operate primarily on the DNA site for inhibition of the cancer cell lines [26,50].

The polymers synthesized by us have shown good ability to inhibit a variety of cancer cell lines Table 1. These cell lines represent all of the major human solid tumor cell lines. These cell lines include resistant cells meaning cell lines that have shown ability to resist treatment with the traditional anticancer drugs [39] (Table 1). Inhibition depends on the metal atom present as well as the nature of the Lewis base. With respect to the metal, in general, inhibition
is of the order Hf>Zr>Ti>Sn>Sb, Bi, As. Inhibition is also dependent on the specific Lewis base. A primary measure of the ability for a drug to inhibit cancer growth is the effective concentration, EC. The 50% effective concentration, EC50, is the concentration of a toxicant, drug, or antibody that induces an inhibitory response halfway between the baseline and maximum after a specified exposure time. The desired outcome is to have low EC50 values as this indicates that only a small concentration of the anti-cancer agent is needed to elicit inhibition. For the compounds described here, once inhibition begins, the slope of the dose/concentration curve is high with inhibition being total. Depending on the specific Lewis acid/base the EC50 value is typically between milligrams/mL to nanograms/mL. The metal-containing compounds are often coupled with a Lewis base that exhibits some biological activity hoping for a syngeneic effect. Drugs that have been employed as the Lewis bases include ciprofloxacin, diethylstilbestrol, cephalaxin, acyclovir, thiamine, dicumarol, camphoric acid, histamine, 2-ketoglutaric acid, salicylic acid, dipicolinic acid, isomanide, glycyrrhetinic acid, phentolamine, thiodiglycolic acid. Lewis bases that themselves exhibit no ability to inhibit cancer can also exhibit good inhibition when coupled with a metal-containing moiety. These include a wide variety of diols such as ethylene glycol, Figure 4 [29,50]. Recently, water-soluble drugs possessing the metal-containing unit were synthesized [29] employing as the Lewis base poly (ethylene glycol), PEG. The resulting water-soluble polymers exhibit good inhibition of the cell lines. Figure 5 contains the reaction between titanocene dichloride and PEG forming water soluble polyethers (Figures 4 & 5).

**Figure 3:** Synthesis of triphenylantimony polyesters from reaction with 3,5-pyridinedicarboxylic acid where R is simple chain extension.

**Figure 4:** Reaction between ethylene glycol and dibutyltin dichloride forming polyethers.

**Figure 5:** Formation of water-soluble polyethers from reaction of titanocene dichloride and various poly (ethylene oxides) where R represents simple chain extension.

**Viruses**

These metal-containing polymers also inhibit a variety of viruses including ones where no current drugs are available for treatment [40,41,49]. Table 2 contains viruses that have been inhibited by our metal-containing drugs including most recently the zika virus. These viruses include both DNA and RNA viruses.
They include several that have been identified as possible weapons of mass destruction, namely the vaccinia virus. Three DNA viruses are effectively inhibited by the metal-containing polymers (Table 2). They are the vaccinia virus used to vaccinate humans against smallpox; herpes simplex virus 1, the virus responsible for over 45 million infections yearly in the US, comprising one of five adolescents and adults; and the varicella zoster virus, also a herpes virus and responsible for chickenpox and shingles. Thus, the metal-containing polymers represent a possible potent approach towards inhibiting unwanted viruses (Table 2).

### Table 1: Caner cell lines inhibited by metal-containing polymers described here.

| Strain Number | NCI Designation | Species | Tumor Origin | Histological Type |
|---------------|-----------------|---------|--------------|-------------------|
| 3465          | PC-3            | Human   | Prostate     | Carcinoma         |
| 7233          | MDA MB-231      | Human   | Pleural effusion breast | Adenocarcinoma |
| 1507          | HT-29           | Human   | Recto-sigmoid colon | Adenocarcinoma |
| 7259          | MCF-7           | Human   | Pleural effusion-breast | Adenocarcinoma |
| ATCC CCL-75   | WI-38           | Human   | Normal embryonic lung | Fibroblast |
| CRL-1658      | NIH/3T3         | Mouse   | Embryo-continuous cell line of highly contact-inhibited cells | Fibroblast |
| ATCC DDL-1658 | WI-38 VA13 2RA  | Human   | Normal embryonic lung transformed with SV-40 virus | Fibroblast |
| L929          | Mouse           | Connective tissue transformed | Fibroblast |
| 143           | Human           | Osteosarcoma bond cells | Fibroblast |
| Vero          | Monkey          | Epithelial cells | Fibroblast |
| AsPC-1        | Human           | Pancreatic cells | Adenocarcinoma |
| PANC-1        | Human           | Epitheloid pancreatic cells | Carcinoma |
| U251          | Human           | Glioblastoma multiforme | Astrocytomas |
| G55           | Human           | Glioblastoma | Astrocytomas |
| ATCC CCL 163  | Mouse           | Embryo-continuous cell line of partially transformed cells | Fibroblast |
| ATCC HTB 75   | Human*          | Ovary   | Adenocarcinoma resistant cells |
| ATCC HTB 161  | Human**         | Ovary   | Adenocarcinoma resistant cells |

From a cancer patient with ovarian cancer that had previously been treated with cytoxan, adriamycin, 5-fluorouracil, and Fur IV. From a cancer patient with ovarian cancer that had been treated with adriamycin, cyclophosphamide, and cisplatin.

### Table 2: Viruses inhibited by metal-containing polymers discussed in this report.

| Virus                  | Disease in humans | Viral genome | Virus replication in cytoplasm or nucleus | Current antiviral drugs (CDC recommendations) |
|------------------------|-------------------|--------------|------------------------------------------|---------------------------------------------|
| Zika virus (502)       | Microcephaly, Guillaun-Barré syndrome (GBS) | Single-stranded RNA | Cytoplasm | None |
| Vaccinia virus (WR)    | Vaccine strain for smallpox | Double-stranded DNA | Cytoplasm | Vaccine, Tecovirimat, Ganciclovir, Brincidofovir |
| HSV-1 (Herpes simplex-1) | Herpes           | Double-stranded DNA | Nucleus | Acyclovir, Valacyclovir, Famciclovir |
| HSV-2 (Herpes simplex-2) | Herpes           | Double-stranded DNA | Nucleus | Acyclovir, Valacyclovir, Famciclovir |
| VZV (Varicella Zoster) | Chickenpox/shingles | Double-stranded DNA | Nucleus | Vaccine, Acyclovir |
| Reovirus               | Respiratory enteric orphan virus | Double-stranded RNA | Cytoplasm | None |

### Why Polymeric Drugs?

A critical question is “Why Polymeric Drugs?” What advantageous do polymeric drugs offer [50-60]. Following briefly describes some advantages. Each of these advantages is related to the size of polymers and what such size offers. First, because of their size, polymers travel through the body, in particular the kidney and bladder, more slowly lessening organ damage allowing the organs to limit the negative effect [50,61]. Second, cancer cells are less cohesive, offering greater porosity, and are not as coherent as normal cells with relatively “rough” exteriors. This allows polymers to have a greater opportunity to be “snagged” by the cancer cells allowing them extended ability to be associated with the cancer cells resulting in a greater ability to inhibit cell...
growth. This scenario is described as the enhanced permeability and retention effect [50,62-64]. Third, increased size allows for a greater designing of the drug increasing its effectiveness [65-69]. This fine tuning includes attachment of “biological homing agents”. Thus, polymeric drugs offer advantageous over small molecule drugs that can be used to more effectively combat unwanted diseases compared to small molecule drugs.

Summary

Metal-containing polymers show ability to inhibit all the major solid tumor cancers as well as important viruses. They are easily synthesized and offer physicians new drugs to attack these harmful illnesses.

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