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INHIBITION OF HUMAN GLIOBLASTOMAS BRAIN CANCER CELL LINES BY METAL-CONTAINING POLYMERS

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ABSTRACT

We have been investigating the inhibition of a variety of human cancers including pancreatic, prostrate, breast, lung, ovary and colon employing metal-containing polymers. Recently we found that we could inhibit human glioblastomas brain cancer cells using these same polymers as well as specially designed polymers containing Lewis bases that themselves cross the brain blood barrier. Here we describe some of these results. These efforts are a precursor to studying brain cancer in live animals and eventually humans. A comparison between the various reactants and their ability to inhibit the human brain cancer cell lines is described.

KEYWORDS: Cancer, inhibition brain cancer, organotin polymers, metallocene polymers, human glioblastoma brain cancer.

Polymers

The advantages of polymers as drugs has been reviewed.[1-14] 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 effects.[1],[15] 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.[1],[15-19] Third, increased size allows for a greater designing

of the drug increasing its effectiveness.[18],[19] This fine tuning includes attachment of "biological homing agents".

The advantages of employing metal-containing moieties has also been reviewed.[1],[2] Briefly they include the following. The metal-containing reactants employed here are all commercially available and have been shown to assist in the inhibition of brain cancer. They allow the ready inclusion of a variety of Lewis bases whose products are found to inhibit all of the main groups of solid cancers. For instance, Lewis bases that contain acids react with acid chlorides, but rather form only hydrolysis products. Whereas, with the employed Lewis bases containing acid functional groups, subsequent to neutralization forming salts, they react forming the desired ester linkages allowing the use of such important reactants as amino acids.

We have a wide variety of drugs that show good inhibition of the two brain cancers employed by us. As in all drug use, the drug must come in contact directly or indirectly with the specific target. While we have attempted to design drugs that may themselves transverse the blood brain barrier, BBB, it is possible that the polymers containing them will not. Lately, potential therapeutic materials for brain cancer have been delivered using systematic intravenous or oral routes and include intracerebroventricular delivery, ICV ports, intranasal routes, as well as implantation therapy. These routes have been reviewed.[20-23]

Cell Lines

Two human brain cancer cell lines were employed in our studies. The U251 is among the most often used. It was established at the Wallenberg laboratory, Uppsala, Sweden about 40 years ago derived from human gliomas, derived from a male patient with malignant astrocytoma. G55 is a human glioblastoma (very aggressive) cell line that has been passed through nude mice and re-established as a stable xenograft cell line. The two cell lines each have unique levels of ATP and respond differently to assays with different tumorgenicity, mutations, and expressions of different genes. Studies show that G55 tends to be more invasive some believing that G55 models are more physiologically relevant because of greater invasiveness and migration since they form invasive intracranial tumors in rodents more characteristic of primary human glioblastoma multiforme ,GBM, the most aggressive form of brain cancer.

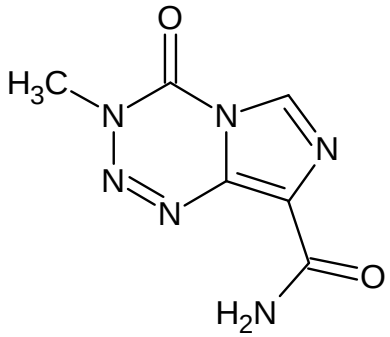
Current Treatments

There exist several types of brain tumors. For primary brain tumors these include gilomas (50%), meningiomas (21%), pituitary adenomas (15%) and nerve sheath tumors (8%).[24] Glioblastomas tumors typically have poor outcomes while meningiomas typically have favorable end points. It is glioblastoma type of cancer that is our initial focus. Treatments include radiation, surgery, and chemotherapy. The typical prognosis is not favorable with a five-year survival rate in the USA of about one third. (In the USA there are about 44,000 new brain tumors yearly (2005) counting for about 2.5% of the cancer-related deaths.

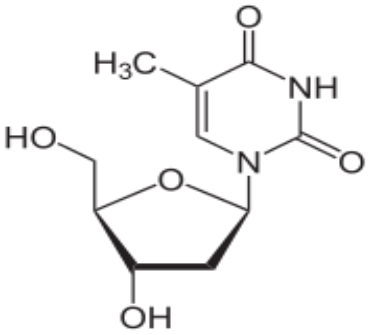
Treatment of brain gliomas is typically a combination of radiation, surgery, and chemotherapy. Cancer chemotherapy is actively being pursued. Briefly, immunotherapy is continually being studied but currently little or no progress has been made to improve life expectancy as of 2015. Beginning in 2000 vesicular stomatitis virus has been used to infect and kill cancer cells without harming healthy cells. More recently retroviral replicating vectors have been employed in the treatment of solid tumors. They are currently undergoing Phase I and II clinical trials for the treatment of glioma. As of 2014 results of these trials have not been reported. Thus, there are few positive results for the positive treatment of brain cancers using chemotherapy. For gliomas, about half survive for one year and one quarter for 2 years.

Temozolomide crosses the blood-brain barrier, BBB, and is being used to treat high-grade brain gliomas tumors.[25] Undesired side-effects are associated with its use and there is little evidence that it greatly improves survival. For recurrent high-grade glioblastoma angiogenic blockers such as bevacizumab has been used with some positive results in conjunction with chemotherapy.[26-29]

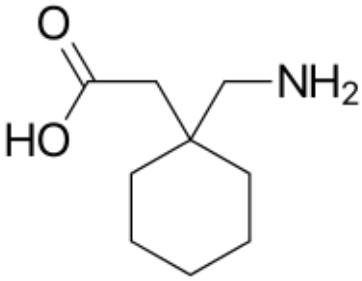
Temozolomide is structurally related to DNA bases. We include in our initial group a thymidine derived polymer that also crosses the BBB and is a DNA base. Further included in the initial group of compounds studied is a gabapentin polymer where gabapentin is also a BBB material. Also, 4-aminobenzoic acid, PBA, involved in folic acid synthesis, is a BBB compound.



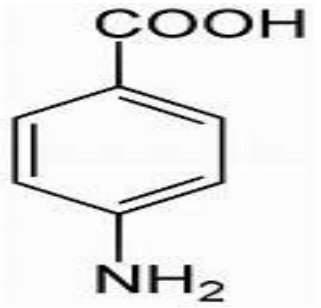
Temozolomide



Thymidine



Gabapentin



4-Aminobenzoic acid

Figure 1: Structures of important Lewis bases.

While the current focus is on brain cancer, these compounds may prove useful in the treatment of other brain related problems including Alzheimer's, dementia, amnesia, autism, epilepsy, stroke, Lupus, cerebral palsy, Parkinson's, etc.

Use of Organotin and Group 4 Metallocenes In Cancer Treatment

For over 80 years' organotin compounds have been known to inhibit cancer cell growth.[29-37] More organotin compounds are available commercially than any other metal-containing organometallic.[38],[39] Further, more organotin compounds have undergone testing as potential anticancer agents than any other single group of compounds.[38] In our work compounds containing dibutyltin unit are often most effective at inhibiting cancer growth. Butyltin monomers have been commercially used for over fifty years, and are the least toxic organotin moiety to humans.[39]

Based on the historical success of organotin monomers, we have synthesized a number of organotin-containing polymers, including the first water soluble organotin (and Group 4 metallocene) polymers with many of them exhibiting wide-spread inhibition of a number of cancer cell lines including those associated with lung, bone, colon, breast, ovarian, and prostate cancer and most recently, pancreatic cancer cell lines.[38],[40-61] These products

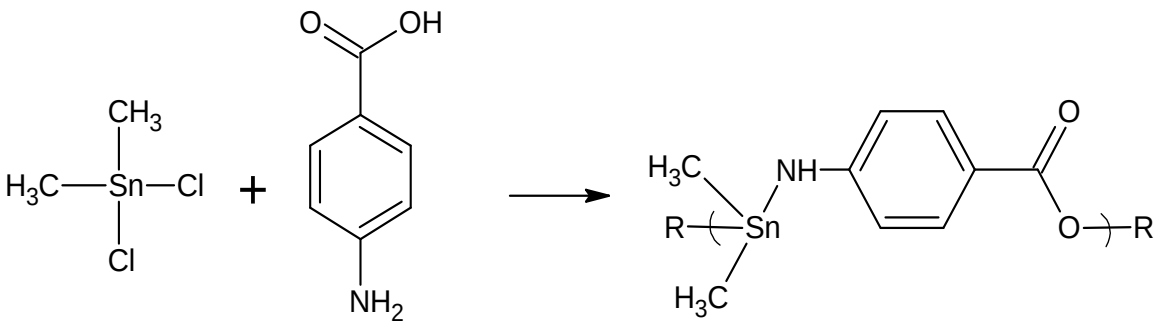
generally exhibit good inhibition of cell growth equal to and greater than that found for cisplatin, one of the most widely employed chemotherapeutic drugs.[62]

The mechanism(s) of action of tin-containing compounds is not well-understood and has been recently summarized as has the advantages of employing polymeric drugs.[45] The locations of activity within these compounds are numerous and these multiple sites may be advantageous in fighting cancer since they may allow curtailment of cancer growth though several mechanisms.

Polymer Synthesis

Synthesis was accomplished employing the interfacial polycondensation process. Reactions are rapid occurring in about 5 seconds employing commercially available reactants allowing for ready scale up for the synthesis of grams to pounds of material. The synthetic procedure, the interfacial polycondensation process, was popularized by Morgan and co-workers and enlarged by Carraher and co-workers.[74-76] This technique is used in the commercial production of polycarbonates and aromatic nylons.[77],[78]

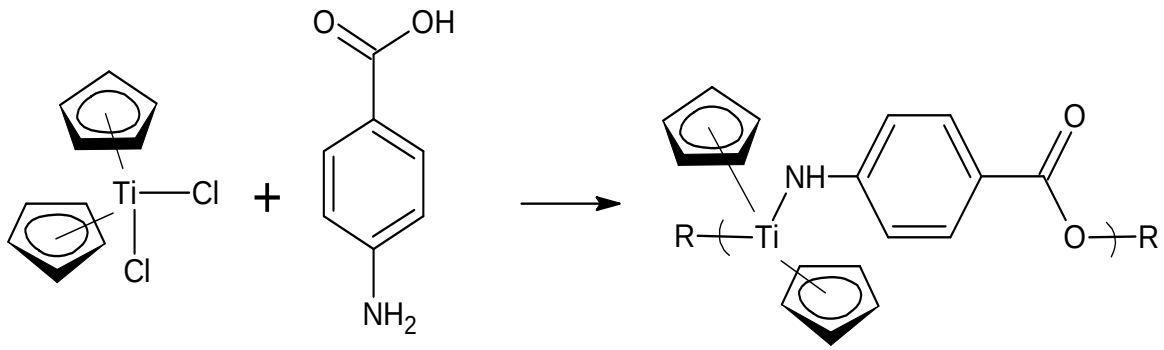
The overall reaction is referred to as a Lewis acid/base condensation reaction. Thus, the production of the polymer from 4-aminobenzoic acid, PABA, with dimethyltin dichloride is shown as Figure 2 where the Lewis acid is the dimethyltin dichloride and the Lewis base PABA.



Dimethyltin Dichloride **PABA** **Polymer Repeat Unit**

Figure 2: Reaction of dimethyltin dichloride and 4-aminobenzoic acid, PABA, where R represents simple chain extension.

The analogous reaction except employing a metallocene reactant, here titanocene dichloride, is shown in Figure 3.



Titanocene Dichloride **PABA** **Polymer Repeat Unit**

Figure 3: Reaction of titanocene dichloride with 4-aminobenzoic acid where R represents simple chain extension.

The mechanism(s) of action of tin-containing compounds is not well-understood and has been recently summarized as has the advantages of employing polymeric drugs.[1] The locations of activity within these compounds are numerous and these multiple sites may be advantageous in fighting cancer since they may allow curtailment of cancer growth though several mechanisms.

Studies are consistent with DNA-metallocene interactions, including titanocene dichloride, zirconocene dichloride, and hafnocene dichloride, being a major determinant in the anticancer activity of these materials.[82]

Two metal-containing products have undergone human cancer testing. The first are derivatives of cisplatin and the second metal is titanium structurally related to titanocene dichloride. It was known as a potential anticancer drug since the later 1970s.[63-66] Initial clinical tests against breast and renal cancer were carried out and were only moderately successful.[67-69] Since then improved derivates have been sought. The most effective is known at titanocene Y derived from fuvenes eventually giving bis-[(p-methoxybenzyl)-cyclopentadienyl[titanium(IV) dichloride.[64],[70] Inhibition activity is related to interaction with the human genome.

A major problem is lack of solubility of the titanocene compounds.[63-69] Our titanocene-containing polymers are soluble in dipolar aprotic solvent such as DMSO and we have

synthesized water-soluble polymers from PEG.[52] Once dissolved, the polymers are stable in aqueous solutions for longer than three months.

The term Group 4 metallocene dichlorides refers to the titanocene, zirconocene, and hafnocene dichlorides. They are widely used in industry as stereoregular catalysts for the production of major polymers such as high-density polyethylene, polypropylene, and polystyrene.[77],[78] The syntheses described in the proposal employ commercially available reactants and the employed synthetic technique is also commercially employed to make aramids and polycarbonates so that scale up is easy.

While we have synthesized a variety of organotin polymers that inhibit the brain cell lines, the overall inhibition for the metallocenes is better so initially the test compounds are from the metallocenes.

Inhibiiton Measures

The two most common measures to evaluate cell line results were used. WI-38 cells were used as the standard cell line. The term effective concentration, EC, is employed as the measure of the concentration needed to effect inhibition-here, specifically the concentration that induces a response halfway between the baseline and maximum, EC_{50}. The second measure is the concentration of drug necessary to inhibit the standard cells compared to the concentration of drug necessary to inhibit the growth of the test cell line, here designated as the chemotherapeutic index, CI, so that the CI_{50} is then the ratio of the EC_{50} for the *WI-38* cells divided by the EC_{50} for the particular cell line, here one of the brain cancer cell lines.

It is desired to have the lowest EC_{50} values since these offer the greatest chance at causing the least damage to the healthy cells. High CI_{50} values are desired since this offers the greatest differentiation between inhibiting the cancer cells compared to the healthy cells.

Structural analysis for the polymers includes light scattering photometry (chain length and molecular weight), FT-infrared spectroscopy, nuclear magnetic resonance spectroscopy, and high-resolution electron impact positive ion matrix assisted laser desorption ionization time of flight, HR MALDI-TOF, mass spectrometry.

INHIBITION RESULTS

Following are results from our studies that show the ability of the polymers to inhibit human cancer cell growth. Table 1 contains results for the metal-containing monomers. In almost all cases, the Lewis base has little or no activity against the cancer cell lines. In each table of inhibition values columns 2,3, and 4 are EC_{50} values and columns 6 and 7 are CI_{50} values. The ability to inhibit the brain cancer cell lines is greater for the polymers compared to the monomers. Thus, the ability to inhibit the brain cancer cell lines is due to the combination. Once inhibition begins it continues with a steep decent to total inhibition.

We have results for over fifty different groups of polymers but have included only results for some that illustrate the general results. In each case, the Lewis bases listed here are known to cross the BBB.

Table 01: Inhibition of brain cancer cell lines by the metal-containing monomers. Concentration units are micrograms/mL. Values given as ( ) are standard deviations.

Monomer	WI-38	U251	G55	CI U251	CI G55
Cisplatin	0.0029(.002)	0.015(.01)	0.021(.01)	0.80	0.57
Cp_2TiCl_2	1.25(.6)	>2	>2	<0.62	<0.62
Cp_2ZrCl2	0.94(.8)	>2	>2	<0.47	<0.47
Cp_2HfCl2	1.2(.7)	>2	>2	<0.60	<0.60
Me_2SnCl_2	0.41(.04)	0.91(.5)	1.2(.6)	0.45	0.31
Et_2SnCl_2	0.38(.04)	1.1(.6)	1.3(.7)	0.34	0.29
Bu_2SnCl_2	0.33(.05)	1.0(.2)	1.0(.4)	0.33	0.33
Oc_2SnCl_2	0.44(.03)	1.3(.7)	0.95(.6)	0.34	0.46
Ph_2SnCl_2	0.29(.03)	0.89(.6)	0.97 (.6)	0.29	0.30

Tables 2 and 3 contain results that allow a ready comparison between the organotin polymers and metallocene products. With respect to the tin polymers with the exception of the diethyltin polymer with thymidine there is little difference between the organotin polymers and the activity towards the human brain cancers with respect to EC_{50} and CI_{50}. With other cancers it is found that the most active organotin is the dibutyltin followed by the diphenyltin moiety. In general, the EC_{50} values are similar for the two brain cancer cell lines for the organotin polymers consistent with the idea that they will be able to inhibit other brain cancer cell lines.

Table 2: Inhibition measure for selected organotin products for specific Lewis bases. Concentration is given in micrograms/mL. Values given in ( ) are standard deviations.

Organotin	Lewis Base	WI-38	U251	G55	CI U251	CI G55
Me_2SnCl_2	Gabapentin	0.36(.7)	0.29(.3)	0,24(.5)	1.2	1.5
Et_2SnCl_2	Gabapentin	0.35(.5)	0.34(.4)	0.28(.5)	1.2	1.5
Bu_2SnCl_2	Gabapentin	0.38(.6)	0.22(.3)	0.32(.5)	1.4	1.0
Oc_2SnCl_2	Gabapentin	0.33(.3)	0.28(.4)	0.24(.5)	1.3	1.5
Ph_2SnCl_2	Gabapentin	0.35(.3)	0.24(.4)	0.30(.4)	1.6	1.3
Me_2SnCl_2	Diglycine	0.67(.05)	0.72(.07)	0.83(.08)	0.93	0.81
Et_2SnCl_2	Diglycine	0.69(.05)	0.65(.05)	0.76(.07)	1.1	0.91
Bu_2SnCl_2	Diglycine	0.64(.05)	0.73(.07)	0.78(.07)	0.88	0.83
Oc_2SnCl_2	Diglycine	0.66(.05)	0.61(.06)	0.63(.06)	1.1	1.0
Ph_2SnCl_2	Diglycine	0.66(.05)	0.67(.05)	0.62(.05)	0.99	1.1
Me_2SnCl_2	Lamivudine	0.37(.06)	0.49(.05)	0.55(.05)	0.76	0.67
Et_2SnCl_2	Lamivudine	0.36(.05)	0.43(.05)	0.49(.05)	0.84	0.73
Bu_2SnCl_2	Lamivudine	0.37(.05)	0.44(.05)	0.47(.05)	0.84	0.79
Oc_2SnCl_2	Lamivudine	0.37(.05)	0.47(.05)	0.49(.05)	0.79	0.76
Ph_2SnCl_2	Lamivudine	0.39(.05)	0.51(.05)	0.54(.06)	0.76	0.72
Me_2SnCl_2	Thymidine	0.45(.05)	0.51((.04)	0.55(.04)	0.88	0.82
Et_2SnCl_2	Thymidine	0.045(.05)	0.23(.04)	0.28(.04)	0.20	0.16
Bu_2SnCl_2	Thymidine	0.46(.05)	0.42(.04)	0.44(.04)	1.2	1.0
Oc_2SnCl_2	Thymidine	0.44(.05)	0.44(.04)	0.49(.04)	1.0	0.90
Ph_2SnCl_2	Thymidine	0.043(.05)	0.35(.04)	0.37(.04)	0.12	0.12
Me_2SnCl_2	PABA	0.54(.04)	0.57(.05)	0.54(.05)	0.95	1.0
Et_2SnCl_2	PABA	0.53(.04)	0.52(.05)	0.61(.05)	1.0	0.89
Bu_2SnCl_2	PABA	0.51(.04)	0.55(.05)	0.62((.06)	0.93	0.82
Oc_2SnCl_2	PABA	0.53(.04)	0.90(.08)	0.91(.08)	0.59	0.58
Ph_2SnCl_2	PABA	0.53(.04)	0.85(.05)	0.83(.08)	0.62	0.64

Comparing the activity of the metallocene there is again little strict trend but within any Lewis base there may be a great difference. Thus, for the thymidine product the EC_{50} and CI_{50} values for the titanocene product are much inferior compared to the products from the zirconocene and hafnocene product with respect to the inhibition of the brain cancers. Comparing the EC_{50} values, the thymidine product from zirconocene and hafnocene exhibit inhibition to the nanogram/mL range. In general, inhibition of the two cancer cell lines is similar again consistent with the ideal that the polymers will show the ability to inhibit other brain cancer cell lines.

With respect to CI_{50} values, the PABA products all show decent values with all exhibiting values near and greater than two. On the average, the CI_{50} values are on the order of Zr=Hf>.Ti. This trend is consistent with most of the polymers thus far tested.

Table 3: Inhibition results for selected Lewis bases for metallocene-containing polymers.

Metallocene	Lewis Base	WI-38	U251	G55	CI U251	CI G55
Cp_2TiCl_2	PABA	0.14(.1)	0.80(.01)	0.10(.03)	0.18	1.4
Cp_2ZrCl_2	PABA	0.42(.2)	0.16(.04)	0.20(.06)	2.6	2.1
Cp_2HfCl_2	PABA	0.46(.3)	0.32(.08)	0.20(.06)	1.4	2.3
Cp_2TiCl_2	Diglycine	0.664(.1)	0.767(.2)	0.614(.1)	0.86	1.1
Cp_2ZrCl_2	Diglycine	0.782(.1)	0.400(.1)	0.609(.1)	2.0	1.3
Cp_2HfCl_2	Diglycine	0.724(.1)	0.659(.1)	0.633(.1)	1.1	1.1
Cp_2TiCl_2	Lamivudine	0.431(.1)	0.508(.1)	0.444(.1)	0.85	0.97
Cp_2ZrCl_2	Lamivudine	0.400(.1)	0.414(.1)	0.406(.1)	0.97	0.99
Cp_2HfCl_2	Lamivudine	0.398(.1)	0.491(.1)	0.483(.1)	0.87	0.49
Cp_2TiCl_2	Thymidine	0.040(.005)	14(.7)	120(.7)	0.0030	0.00033
Cp_2ZrCl_2	Thymidine	0.046(.005)	0.026(.003)	0.0035(.003)	1.8	1.3
Cp_2HfCl_2	Thymidine	0.043(.005)	0.062(.003)	0.071(.003)	0.69	0.61
Cp_2TiCl_2	PABA	0.48(.04)	0.19(.02)	0.21(.02)	2.5	2.3
Cp_2ZrCl_2	PABA	0.50(.04)	0.26(.02)	0.30(.02)	1.9	1.7
Cp_2HfCl_2	PABA	1.2(.2)	0.22(.02)	0.34(.02)	5.5	3.5

On the average, the values for EC_{50} are less, that is, inhibition at lower concentrations, for the metallocenes compared with the organotin and the CI_{50} values are greater for the metallocene products. Further, the CI_{50} values are generally greater for the polymers compared to values found for cisplatin. While cisplatin and other platinum drugs are widely used to treat a variety of cancers it is highly toxic with a large variety of unwanted side effects.[62] They are more toxic than either the organotins and metallocenes.

There is sufficient variation in the values as the Lewis base is varied to encourage further research to seek polymers that show smaller EC_{50} and larger CI_{50} values. This hunt continues.

CONCLUSIONS

In summary, both the metallocene and organotin polymers exhibit good inhibition of the brain cancer cell lines with the metallocene polymers generally showing lower EC_{50} and higher CI_{50} values.

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