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Might Actinomycin be Used to Cure All Cancer?

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In addition to curing Wilm's tumor and choriocarcinoma, I propose actinomycin to be more widely used to cure ALL cancer – i.e., curing lung, colon, breast, ovarian and other cancers – for reasons described in this communication.

The discovery that actinomycin is a powerful anticancer agent against Wilm's tumor and choriocarcinoma was made by Sidney Farber in the early 1950s. This miraculous discovery is known to dramatically cure patients suffering from both embryonic tumors -- and still remains the treatment of choice to this day!

Although it is not known whether actinomycin can be used to cure ALL cancers -- the purpose of this paper is to call attention to the possibility that trace amounts of actinomycin given over an extended period of time could prove to be a powerful anticancer chemotherapeutic regimen. It is important that the medical community realize this, and to understand how actinomycin acts to defeat cancer.

Background Information

Actinomycin D is a naturally occurring cyclic polypeptide containing antibiotic known to bind to DNA and inhibit RNA synthesis (see Figure 1) [1–4]. It does this by interfering with the elongation of growing RNA chains by the RNA polymerase enzyme [5]. Nucleolar 5-S ribosomal RNA synthesis is known to be particularly sensitive to the presence of actinomycin, and this accounts for its pharmacological activity as well as its extreme toxicity to mammalian cells [6, 7].

Stereochemistry of Actinomycin-DNA Binding

Several years ago, we determined the three-dimensional structure of an actinomycin-deoxyguanosine complex by x-ray crystallography [8–11]. The stereochemical information obtained from this study suggested a model to understand the general features of how actinomycin binds to DNA. According to this model, the phenoxazone ring system on actinomycin intercalates between adjacent guanine-cytosine base-pairs, while pentapeptide chains lie in the narrow groove of the B-helix to form hydrogen bonds with guanine residues on opposite chains. Implicit in this model was the assumption that actinomycin binds to B-DNA, or to a distorted B-DNA form. The possibility that actinomycin binds to some other discretely different DNA conformational state was not envisioned at that time.

A modification to this actinomycin-DNA binding model was subsequently proposed, which allows one to understand its mechanism of action (see Figure 2). This model is similar to the previous one, however it predicts actinomycin to bind to (what we have called) beta-DNA (i.e., not to B-DNA), this being a metastable and hyperflexible premelted form inferred from our wider crystallographic studies of planar drug molecules intercalated into a series of DNA-like and RNA-like self complementary dinucleoside-monophosphates [12-14].

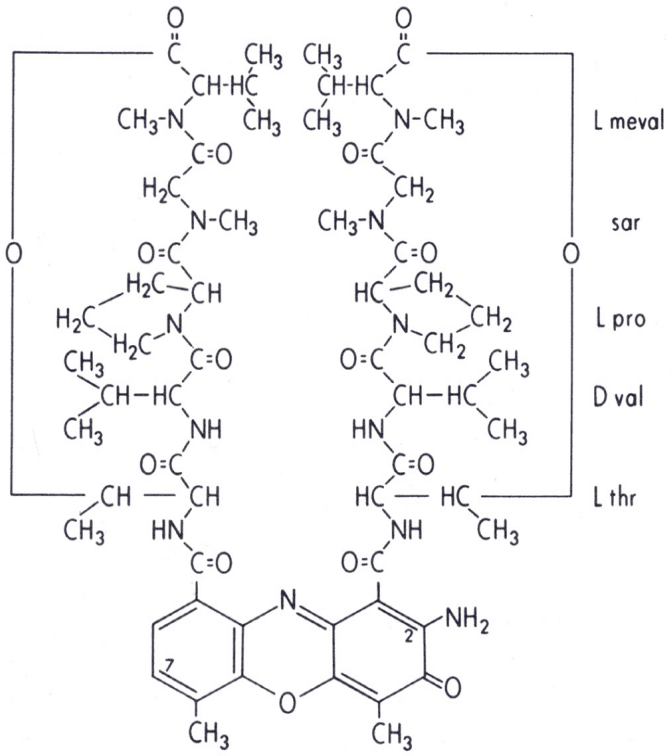

Figure 1. Chemical structure of actinomycin D. Abbreviations (L meval, L methyl valine; sar, sarcosine; L-pro, L proline; D-val, D valine; L thr, L threonine)

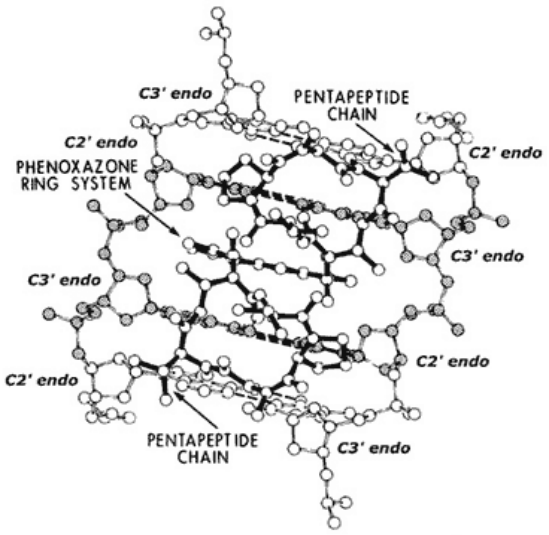

Figure 2. Actinomycin: beta-DNA binding model.

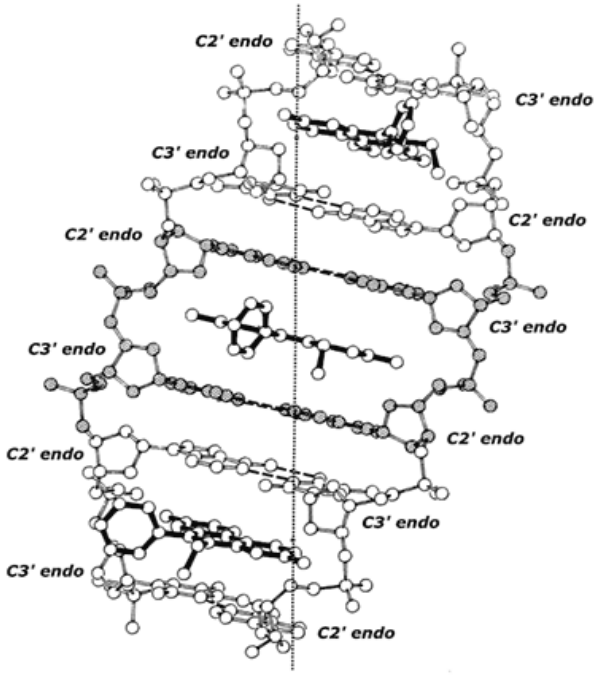

Figure 3. Ethidium: beta-DNA binding model.

Figure 3 shows this same (extended) beta-DNA structure "pinned" by ethidium. The complex is an organized right-handed double helical structure in which the beta-structural element plus the intercalator form the asymmetric unit of the helix. This maximally elongated and unwound DNA duplex-structure, pinned by ethidium at saturating concentrations, readily explains the well-known observation of neighbor-exclusion intercalative drug-binding [15–17].

Mechanism of Action of Actinomycin D

I have next proposed beta-DNA to be an obligatory intermediate (i.e., a transition-state intermediate) in DNA-melting. This concept readily leads to understanding the mechanism of action of actinomycin D.

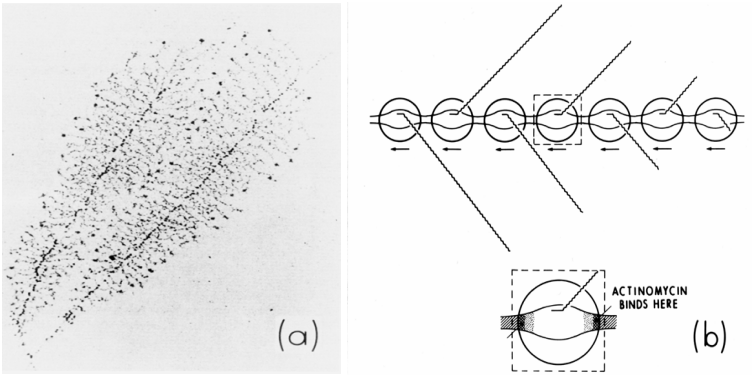

Figure 4. (a) Electron-micrograph of nucleolar 5-S ribosomal-RNA genes undergoing very active transcription within dividing amphibian oocytes [18]. (b) Interpretation of this photomicrograph showing how actinomycin acts to inhibit this process. Actinomycin binds to beta-DNA, a conformational intermediate that exists within the boundaries connecting double-stranded B-DNA with single-stranded DNA in the transcription complex. This immobilizes (i.e., "pins") the complex, interfering with the elongation of growing RNA chains.

Figure 4 (a) shows an electron-micrograph of nucleolar 5-S ribosomal-RNA genes undergoing very active transcription within dividing amphibian oocytes [18], and my interpretation of this process b), which indicates the mechanism of action of actinomycin D [19, 20].

Actinomycin intercalates into beta-DNA found within the boundaries connecting double-stranded B-DNA with single-stranded DNA in the transcription complex. This immobilizes (i.e., "pins") the complex, interfering with the elongation of growing RNA chains. In extremely active genes such as these, RNA polymerases lie in a close-packed arrangement along DNA. Interference with the movement of one polymerase by actinomycin is expected to inhibit the movement of other polymerases. This predicts nucleolar 5-S ribosomal RNA synthesis to be extremely sensitive to the presence of actinomycin [21 - 25].

Might actinomycin be expected to preferentially kill malignant cells?

Nucleoli within each nucleus in malignant cells (such as Hela-cells) are expected to contain large numbers of tandem repeats of 5-S ribosomal genes undergoing DNA-transcription. This is because malignant cells (i.e., being rapidly dividing) require increased numbers of ribosomes to carry out protein synthesis and, for this reason need many more tandem repeats of 5-S ribosomal genes per nucleoli than normal cells (or alternatively, it is possible that each nucleus within a malignant cell contains many more nucleoli than normal cells, the number of tandem repeats of 5-S ribosomal genes in each nucleolus remaining the same).

The presence of very active 5-S ribosomal genes undergoing transcription in malignant cells explains why actinomycin is such a powerful weapon against cancer. Trace amounts of actinomycin given over an extended period of time is expected to be a powerful anticancer chemotherapeutic regimen. Of course, it is necessary to carry out appropriate experiments in mice or in other related mammals before attempting clinical use.

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24. Leroy Liu and James Wang have provided a key insight into the nature of DNA supercoiling accompanying transcription that has shed additional light on this question. They have theorized that – in the presence of significant resistance to the rotational motion of the RNA polymerase and its nascent RNA chain around DNA during transcription – the advancing polymerase generates positive superhelicity in the DNA template ahead of it, and negative superhelicity behind it. In nucleolar genes, where there may as many as 200 RNA polymerases moving down the DNA template while synthesizing growing ribosomal RNA-chains, positive and negative superhelical DNA regions between them annihilate one-another, causing adjacent chains to bond-together to form “trains” of transcription complexes, these now moving synchronously along DNA. If this were the case, then the binding by one actinomycin molecule is sufficient to stop the entire “transcription-train” from moving along DNA.
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