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Topoisomerases as Anticancer Targets

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Abstract

Many cancer type-specific anticancer agents have been developed and significant advances have been made toward precision medicine in cancer treatment. However, traditional or non-specific anticancer drugs are still important for the treatment of many cancer patients whose cancers either do not respond to or have developed resistance to cancer-specific anticancer agents. DNA topoisomerases, especially type IIA topoisomerases, are proven therapeutic targets of anticancer and antibacterial drugs. Clinically successful topoisomerase-targeting anticancer drugs act through topoisomerase poisoning, which leads to replication fork arrest and double-strand break formation. Unfortunately, this unique mode of action is associated with the development of secondary cancers and cardiotoxicity. Structures of topoisomerase-drug-DNA ternary complexes have revealed the exact binding sites and mechanisms of topoisomerase poisons. Recent advances in the field have suggested a possibility of designing isoform-specific human topoisomerase II poisons, which may be developed as safer anticancer drugs. It may also be possible to design catalytic inhibitors of topoisomerases by targeting a certain inactive conformations of these enzymes. Furthermore, identification of various new bacterial topoisomerase inhibitors and regulatory proteins may inspire the discovery of novel human topoisomerase inhibitors. Thus, topoisomerases remain as important therapeutic targets of anticancer agents.

1. Introduction

DNA topoisomerases are responsible for DNA unlinking and these ubiquitous enzymes play critical roles in many biological processes involving DNA [1–7]. There are two types of DNA topoisomerases, type I and type II. Type I topoisomerases break one DNA strand of duplex DNA to allow either the passage of the other DNA strand through the break or the

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rotation of downstream DNA duplex about the break, and then reseal the broken strand. As a result, they alter the linking number in steps of one [1–7]. There are three subtypes of type I topoisomerases: type IA, type IB, and type IC. Type IA topoisomerases require a nick or a single-stranded region to bind to DNA [8,9]. They cleave one strand of duplex DNA, covalently attach the active-site tyrosine to a 5′-phosphoryl group, and utilize the 'strand passage' mechanism to alter DNA topology [10,11]. In contrast, types IB and IC topoisomerases cleave one strand of duplex DNA, covalently attach its active-site tyrosine to a 3′-phosphoryl group, and utilize the 'swivel' mechanism to relax DNA supercoils [12]. Bacterial topoisomerase I (Top 1) and topoisomerase III (Top 3) are type IA topoisomerases. Eukaryotic Top 1 belongs to the type IB subtype, and topoisomerase V found in the archaeal genus *Methanopyrus* is, thus far, the only member of the type IC subtype [13]. It is noteworthy that type IB topoisomerases are found in some bacteria [14]. Type II topoisomerases alter the linking number in steps of two by breaking both DNA strands of duplex DNA [referred to as the 'Gate (G)-segment'], passing another duplex DNA [referred to as the 'Transfer (T)-segment'] through the break or the 'DNA gate', and then resealing the broken DNA strands [15–18]. Type II topoisomerases go through a series of large conformational changes when catalyzing the reaction by the 'strand passage' mechanism. When type II topoisomerases cleave two DNA strands, they form phosphotyrosyl bonds between the two active-site tyrosines and a pair of 5′-phosphates to ensure the integrity of DNA can be restored. There are two subtypes of type II topoisomerases, type IIA and type IIB. Topoisomerase VI belongs to the type IIB subtype [19], while all other type II topoisomerases belong to the type IIA subtype. Each subtype of topoisomerase is structurally and functionally conserved and forms a protein family [1–7].

Upon its discovery [20], DNA gyrase was identified as the cellular target of the coumarin and the quinolone antibacterial drugs [21–23]. Since then, DNA topoisomerases, especially type IIA topoisomerases, are recognized as therapeutic targets of many anticancer and antibacterial drugs [6, 24–31]. Several antibacterial agents, including fluoroquinolones, target the bacterial type IIA topoisomerases, DNA gyrase and topoisomerase IV (Top 4). Both human Top 1 (hTop 1) and the two isoforms of human topoisomerase II (hTop 2) are the cellular targets of clinically important anticancer drugs. A large number of small molecules have been identified as inhibitors of hTop 1 or hTop 2. Many of them have been tested in clinical trials, but only a few have enjoyed clinical success. Manipulation of enzyme activities to achieve therapeutic effects has been accomplished by the following mechanisms: (1) suppressing enzyme activity by catalytic inhibitors; (2) activating enzyme activity toward the bona fide or a surrogate substrate; (3) turning the enzyme into a poisonous agent that is toxic to cells. Interestingly, many clinically successful inhibitors of hTop 1 and hTop 2, as well as bacterial type IIA topoisomerase inhibitors, utilize mechanism 3, which is often referred to as 'topoisomerase poisoning' [6, 24–31]. These topoisomerase poisons convert a topoisomerase into a cellular poison by trapping a covalent topoisomerase-DNA catalytic intermediate as a topoisomerase-drug-DNA ternary complex. Topoisomerase poisoning is often caused by the inhibition of the religation reaction [32], which is also supported by the structural studies of topoisomerase-drug-DNA ternary complexes [33,34]. However, some topoisomerase poisons, including spontaneous DNA damage and fluoroquinolones, have reported to stimulate the strand breakage reaction [35–38]. Thus,

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mechanism 2 appears to be used by some topoisomerase inhibitors to poison their target. Ternary complex formation triggers cytotoxic events, which include the inhibition of DNA replication, the generation of double-strand breaks (DSBs), and subsequent cell death [6, 24–31]. The catalytic inhibitors of either hTop 1 or hTop 2 that utilize mechanism 1 have not seen much success in clinical applications. One possible explanation is that elevated levels of topoisomerases in cancer cells would reduce the efficacy of catalytic inhibitors. In contrast, elevated levels of topoisomerases would increase the potency of topoisomerase poisons [39]. We recently discovered novel quinolones that inhibit both hTop 1 and hTop 2 without poisoning them [40]. These compounds exhibited promising *in vitro* and *in vivo* anticancer activities. Thus, catalytic inhibitors that are capable of inhibiting multiple human topoisomerases may be developed as potent anticancer drugs [27,30]. The development of enzyme activity modulators can benefit from a detailed understanding of the catalytic mechanisms of the target enzymes. For topoisomerases, structural biology has proven particularly helpful in elucidating not only the enzymes' catalytic mechanisms [1,3,6,41], but also validating the actions of clinically important drugs that specifically target these essential enzymes [33,34,42–44].

New bacterial topoisomerase inhibitors (NBTIs) [45,46], as well as toxins and regulatory proteins that target DNA gyrase [26], are also described in this review because their novel binding sites and modes of action to modulate the activities of bacterial type IIA topoisomerases may inspire the discovery of new anticancer drugs that act on hTop 2. In addition to the α and β form of hTop 2 (hTop 2α and hTop 2β), type IIA topoisomerases, and two type IB topoisomerases found in the nucleus (hTop 1) and mitochondria (mTop 1), human cells also have two isoforms of Top 3 (hTop 3α and hTop 3β), type IA topoisomerases [1–7]. However, no inhibitor of human Top 3 has been reported. Thus, we excluded type IA topoisomerases from this review. Our review focuses on recent structural studies of topoisomerase-drug-DNA ternary complexes that have advanced our understanding of the molecular basis of topoisomerase poisoning. Thus, we would like to refer readers to other outstanding reviews on topoisomerases [such as 1–7,41] and topoisomerase inhibitors [such as 24–30,44,45] for comprehensive overviews of the many essential studies that have broadened our understanding of the cellular functions and catalytic mechanisms of topoisomerases, as well as topoisomerase-targeting anticancer drugs in discovery and development stages. We apologize to the many colleagues whose work is only briefly discussed or excluded due to space limitations.

2. Cellular functions of topoisomerases

(1) Type IB topoisomerases

The swivel function of eukaryotic Top 1 is essential for removing DNA superhelical tension that arises during both DNA replication and transcription [47–52]. Interestingly, Top 1, but not its catalytic activity, is required for activation of transcription [49,50,53]; however, the topoisomerase activity of Top 2β is required for transcription [54,55]. In human cells, activities of hTop 1 and RNA polymerase II are coupled [56]. Studies on the effect of camptothecin, a Top 1 poison, have demonstrated that efficient expression of long genes requires both Top 1 and Top 2β [57–59].

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mTop I is the only topoisomerase exclusively targeted to mitochondria [60]. However, a long Top 3α isoform produced by an alternative, upstream translation initiation site [61], as well as Top 2α and Top 2β, have also been found in mitochondria [62,63]. mTop 1 plays critical roles in transcription and DNA replication of circular mitochondrial DNA [64,65]. Although cells manage to survive in the absence of mTop 1, loss of mTop 1 severely affects mitochondrial integrity and energy metabolism, [66,67]; however, the presence of Top 3α in mitochondria likely contributes to this survival [61,63,68].

(2) Type IIA topoisomerases

DNA gyrase is the only topoisomerase that is capable of introducing negative supercoils [1–7], while Top 4 is primarily responsible for decatenating daughter chromosomes [69–71]. Bacterial chromosome is kept at a certain negative superhelicity by the balance between the relaxation activity of Top 1 and the supercoiling activity of DNA gyrase [72]. Lower eukaryotes have one type IIA topoisomerase, Top 2, whose structure (note that Top 4 and Top 2 differ in their C-terminal domains) and function are similar to that of Top 4 [1–7, 41]. One distinct difference between bacterial and eukaryotic type IIA topoisomerases is that bacterial enzymes are A_2B_2 heterotetramers, whereas eukaryotic enzymes are homodimers. Bacterial type IIA topoisomerases have been shown to maintain activity when the two subunits are fused into a single peptide [73,74]. Thus, a heterotetrameric type II topoisomerase can be converted into a homodimeric type II topoisomerase by gene fusion.

Unlike lower eukaryotes, mammals have two isoforms of Top 2, Top 2α and Top 2β [75,76]. These isoforms share roughly 70% amino acid sequence similarity and exhibit similar catalytic activities, but they have distinct cellular functions [1–7]. Top 2α is required for DNA replication and chromosome segregation [77–80], and its expression is significantly elevated in proliferating and cancer cells [81–84]. Thus, hTop 2α serves as a biomarker for some cancers. In contrast, Top 2β plays critical roles in transcription in normal mitotic and postmitotic cells, as well as in cancer cells [54,55,81]. In addition, it is also required for development and the survival of some neural cells [85–87].

3. Structural studies of topoisomerases

(1) Type IB topoisomerases

Compared to relaxed DNA that is in the lowest energy conformation, both positively and negatively supercoiled DNA molecules are in higher energy states due to the existence of torsional strains in these structures. In a simple three-step process that does not require additional input of energy, type IB topoisomerases effectively harvest the free energy stored as DNA supercoils to return these energetically strained DNA molecules to their relaxed forms [1–3,6]. This relaxation reaction starts with the catalytic tyrosine-mediated nucleophilic attack on a scissile phosphodiester bond in a DNA duplex, which results in the formation of a transient single-strand break composed of a 3′-linked phosphotyrosyl bond and freed 5′-OH [88–94]. The tension resulting from DNA supercoiling can be dissipated via rotation of the DNA molecule about the break (Fig. 1). Finally, the cleaved phosphodiester bond is resealed and the catalytic tyrosine is regenerated, resetting the enzyme for the next relaxation event.

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Structural analyses of hTop 1 in covalent and noncovalent complexes with DNA suggested that the postulated DNA rotation during the catalytic cycle is likely achieved via a "controlled rotation mechanism" [89,95,96]. Briefly, the catalytic core of type IB topoisomerases is composed of a Cap domain and a catalytic (CAT) domain, which was first observed in tyrosine recombinases [88,97], and these two domains clamp around the DNA duplex upstream to the cleavage site. The DNA upstream of the single-strand break is tightly bound through several protein–DNA interactions between the core of Top 1 and DNA, primarily to the phosphate backbone of the DNA, and is thus unable to rotate. In contrast, the DNA downstream of the break is only loosely held by the nose cone of the Cap domain and linker regions of CAT domain. Conceivably, this weak protein-DNA interface can be easily ruptured by the stored superhelical tension, and the downstream DNA can then rotate about the cleavage site by one or more turns until all torsional strains are released or the break is resealed. Given the limited number of DNA-interacting residues, it appears to be difficult for the enzyme to capture the downstream DNA in the presence of high superhelical tension. Nevertheless, this interface may be re-established at lower superhelical density, which halts the rotating DNA and places the 5′-OH in a favorable position for engaging in the religation reaction [90,98,99]. The rotation and orientation of downstream DNA is 'controlled' by the enzyme, as opposed to random rotation, which would complicate the religation reaction [89].

Types IA, IB, and IIA topoisomerases have distinct requirements of Mg^{2+} for their catalytic activities [100–104]. Structural analysis of the enzyme-DNA covalent complex revealed why type IB topoisomerases do not require a divalent cation for their activity [88]. The transesterification reaction catalyzed by topoisomerases is known to proceed through a high-energy bipyramidal transition state in which two oxyanions are attached to the pentavalent phosphorus. Unlike types IA and IIA topoisomerases, which utilize Mg^{2+} as an essential cofactor for electrostatic stabilization of the transition state [100–102], type IB topoisomerases and members of the tyrosine recombinase family employ positively charged Arg and Lys residues for this purpose [88,97,105].

(2) Type IIA topoisomerases

Even before the first crystallographic visualization of type IIA topoisomerases was available [18,106,107], a series of elegant biochemical studies had established that type II topoisomerases change the linking number of DNA through a 'two-gate' mechanism [108–112]. According to this mechanism (Fig. 2) [1–6,41], the catalytic cycle of type IIA topoisomerases starts from the binding of the G-segment DNA to the enzyme, a process corresponding to the assembly of the so-called 'DNA gate' [44,113]. The formation of such a topoisomerase-DNA binary complex allows both strands of the G-segment to be cleaved via Mg^{2+}-dependent transesterification reactions occurring between the catalytic tyrosine residues and the DNA backbone's phosphodiester bonds [113–115], which introduces a reversible DSB into the G-segment. When a DSB is formed, the DNA backbones are unlocked and the two halves of the G-segment can move apart from each other. This potentiates the DNA gate to enter an open state in which the gap between cleaved DNA ends is spacious enough for the T-segment to be passed through. The incoming T-segment approaches the DNA gate by going through the entry gate located on one end of a type IIA

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topoisomerase (the N-terminal end of eukaryotic Top 2) and moving along the DNA-conducting path that is used by the G-segment to reach its binding surface. After passing through the DNA gate, the T-segment is directed toward, and eventually released from, the exit gate at the other end of the topoisomerase (the C-terminal end for eukaryotic Top 2) [1–6,41]. This unidirectional DNA transport mode is referred to as being 'two-gated' because the entry and exit of T-segment is mediated via two distinct protein gates of type IIA topoisomerases.

A more detailed depiction of the catalytic mechanisms of type IIA topoisomerases would require the following aspects to be addressed in structural terms: (1) the enzyme's overall architecture and spatial domain organization; (2) the assembly of a protein-linked DNA gate; (3) strand breakage of the bound G-segment to unlock the DNA backbones; (4) capture of the T-segment; (5) conformational changes associated with the DNA gate; (6) release of the T-segment and resealing of the cleaved G-segment; and (7) resetting the enzyme conformation for the next catalytic cycle. Thanks to a large number of crystal structures obtained for various fragments of type IIA topoisomerases and two catalytically competent type IIA topoisomerases, which represent structural snapshots of different regions of type IIA topoisomerases at distinct stages of the catalytic cycle, we have obtained valuable insights into each of these steps [1,3,6,41].

All type IIA topoisomerases exhibit a two-fold symmetric architecture with the constituting domains appearing in pairs [1,3,6,41]. The entry gate is formed by two GHKL ATPase domains [116], which are known to dimerize upon ATP-binding, but dissociate in the nucleotide-free state [106,108,117,118]. With gate closure and opening being controlled by ATP, the gate appears to act as a nucleotide-operated protein clamp suitable for T-segment capture. Structural analyses revealed that each nucleotide binding pocket is formed by elements from both ATPase domains; ATP would thus promote dimerization by 'gluing' the two domains together [106,108,117,118]. Although each type IIA topoisomerase possesses two structurally equivalent ATP binding sites, it has been shown that one ATP is sufficient to lock the entry gate in the closed state [119–123]. This finding suggests that, once closed, the entry gate would not re-open until the end of the catalytic cycle when both bound ATP molecules are hydrolyzed (Fig. 2).

The DNA gate is compositely formed by a type IIA topoisomerase and G-segment DNA. The protein part of the DNA gate is composed of two copies of each of the following domains: the topoisomerase-primase (Toprim) domain, winged-helix domain (WHD), and a so-called 'tower' domain [124]. The Toprim domain adopts a Rossmann-like fold and contains a Mg^{2+}-coordinating DXD motif that is essential for the transesterification reaction [125]. The WHD domain is central to type II topoisomerase functions by harboring a helix-turn-helix DNA-binding motif and the catalytic tyrosine residue [18,126]. The tower domain provides additional DNA-binding residues and is an integral part of the DNA gate [124,127]. Crystal structures of the DNA gate in its closed state revealed that all these domains contribute to the formation of a G-segment binding groove, with the WHD domains at the bottom and the Toprim and tower domains lining the sides [44,122–124,127–129]. The bound G-segment is primarily anchored by interacting with the helix-turn-helix motifs of the WHD domains and is bent into a U-shape by a pair of conserved isoleucine residues that

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intercalate into DNA at sites 12 base pairs apart [126]. Basic residues from the tower domains interact with the DNA backbone, presumably to stabilize the bent conformation of the G-segment. The DNA duplex enclosed within the two intercalating residues is distorted toward the A-form, which likely places the scissile phosphodiester bonds, the active site tyrosine residues, and the catalytic Mg^{2+} ions at an optimal orientation for engaging in the transesterification reactions [44,123,124,129]. A structural feature unique to the DNA gate is that, to perform strand breakage and religation reactions, the catalytic tyrosine of one subunit must team up with the Mg^{2+} presented by the Toprim domain of the opposing subunit [44,123,124,127–129]. Therefore, closure of the DNA gate is a prerequisite for the phosphotyrosyl bond to be reactive, and the decoupling between these two catalytic modules would protect the covalent tether from being attacked by nucleophiles present in the vicinity.

The exit gate corresponds to the C-terminal dimerization interface that is usually observed in the closed state [33,42–44,113,123,128,129]. It is expected that the opening of exit gate would be a transient event during the catalytic cycle and the conformational equilibrium associated with the gate should be biased toward the closed form, because premature gate opening would significantly alter the overall architecture of a type IIA topoisomerase and may prevent the cleaved G-segment from being religated. Nevertheless, opening of the exit gate has been visualized by crystallography in the absence of a T-segment [34,124,127].

The structures of a fully active type IIA topoisomerase showed that the DNA gate is sandwiched between the entry and exit gates, an arrangement that agrees fully with the proposed two-gate mechanism [113,129]. In addition, a cavity is observed on each side of the DNA gate, suggesting that the T-segment may be temporarily held within the enzyme during its transportation. These structures also revealed that the DNA gate is connected to the entry and exit gates via the transducer domains and coiled-coil regions, respectively [113,129]. These bridging elements are thought to mediate allosteric communications between the gates. For example, the conformational changes induced by ATP hydrolysis may alter the structure of a DNA gate via the rearrangement of the transducer domain. Also it has been shown that conformations of the DNA and exit gate may be coupled by adjusting the kink of the coiled-coil region. However, more conformational states of type IIA topoisomerases, such as the opening of DNA gate, would be required to understand how the opening and closing of these gates are coordinated.

4. Mechanisms of type IB topoisomerase poisoning

hTop 1 is the cellular target of the quinoline alkaloid camptothecin and its clinically active derivatives, topotecan and irinotecan (Fig. 1) [130–133]. Similar to Top 2 poisons, these drugs trap the Top 1-DNA covalent complex and convert the enzyme into a cytotoxic covalently-linked protein adduct on DNA [6,28,30], which causes the inhibition of DNA replication and the generation of a DSB [134,135]. Crystal structures of the camptothecin and topotecan-bound enzyme-DNA covalent complexes revealed the intercalation of a drug molecule between the cleaved DNA ends [136,137]. Specifically, the A~D rings of the pentacyclic drug stack against base pairs flanking the strand breakage site, and the quinoline nitrogen of B-ring and polar/charged groups of E-ring form hydrogen bonds or salt bridges with nearby amino acid residues. It has been demonstrated that the E-ring exists in

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equilibrium between lactone (closed-ring) and carboxylate (open-ring) forms under physiological condition [138]. Given that E-ring is not involved in base-stacking interactions, and that both forms can be modeled equally well into the electron density of topotecan to provide favorable protein-drug interactions, it appears that opening and closure of the E-ring does not alter the drug's efficacy [139,140]. The strand breakage site-specific drug binding physically blocks the religation reaction [136,137]. The Top 1-catalyzed relaxation reaction is also impaired [141] because the stacking interactions between the bound drug and 5′-base pair about the scissile phosphate would increase the threshold energy for the downstream DNA to rotate.

The anticancer agents indolocarbazoles and indenoisoquinolines also act as hTop 1 poisons [142–147]. Structural analysis showed that the planar polycyclic cores of these compounds intercalate at the strand breakage site, resembling the binding mode of camptothecin [148]. The branching moieties, on the other hand, form distinctive and chemotype-specific protein-drug interactions. Collectively, the observed changes in protein structure and drug-interacting amino acid residues in response to different drugs revealed the landscape and flexibility of the drug-binding pockets. This information should facilitate the development of new type IB topoisomerase poisons. Interestingly, no catalytic inhibitor of type IB topoisomerases has been reported thus far. The structure of hTop 1 in complex with a DNA duplex containing an 8-oxoG lesion suggests the enzyme may adopt an inactive conformation in which the catalytic tyrosine bends away from the active site [149]. Any compounds that bind and stabilize this conformational state of hTop 1 may act as effective catalytic inhibitors. However, the clinical relevance of developing such Top 1 inhibitors has remained to be elucidated.

5. hTop 1-targetting anticancer drugs

Camptothecin (Fig. 3) is a plant alkaloid that poisons hTop 1 [130–133]. Clinical development of camptothecin was discontinued because of its intolerable adverse effects and low therapeutic index [150–152]. However, derivatives of camptothecin, topotecan and irinotecan (Fig. 3), are currently used in the clinic [153–155]. Unfortunately, their clinical use is limited due to their dose-limiting toxicity, especially neutropenia, myelosuppression, and diarrhea [156–161], as well as chemical instability due to the rapid opening of the E-ring [162–164]. mTop 1 is inhibited by camptothecins [60] and mTop 1 can be targeted by topotecan, but not by camptothecin, *in vivo* [165,166]. It is not clear, however, if the effect of camptothecins on mTop 1 contribute to the anticancer activities of these drugs.

(1) Camptothecins

a. Topotecan—Topotecan (Hycamtin) (Fig. 3) is a semi-synthetic water-soluble derivative of camptothecin [167]. It was the first hTop 1 inhibitor approved for oral administration [168,169]. It is often used to treat ovarian and small cell lung cancer [153–155,169].

b. Irinotecan—Irinotecan (CPT-11, Campostar) (Fig. 3) is another water-soluble derivative of camptothecin [170,171]. It is a prodrug and is converted to a biologically active metabolite, ethyl-10-hydroxy-camptothecin (SN-38), by a carboxylesterase [172,173].

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Irinotecan, together with fluorouracil, is often used for the treatment of advanced colorectal cancer [153–155,174].

(2) Non-camptothecins

Camptothecins are the only hTop1 inhibitors approved for clinical use. Despite their effectiveness, these drugs have limitations due to their instability and severe side effects, as well as drug resistance caused by P-glycoprotein [175,176]. To overcome these limitations, non-camptothecin hTop 1 inhibitors have been developed and investigated [177–180]. Among them, indolocarbazoles (NB-506) [142–144], indenoisoquinolines [145–147], and dibenzonaphthyridinones (ARC-111) [181–183] are under clinical development.

a. Indolocarbazoles—Indolocarbozoles are synthetic analogs of antibiotics isolated from several actinomycetes [184]. NB-506 is a DNA intercaltor that can poison hTop 1 [142,143]. NB-506 and camptothecins share the binding site on hTop 1 but hTop 1 is not the only target of NB-506 [185]. Edotecarin (J-107088) is a derivative of NB-506 that does not intercalate into DNA [144]. Similar to NB-506, it poisons hTop 1 but its effect on an unidentified target(s) also contributes to its promising anticancer activity [144].

b. Indenoisoquinolines—Indenoisoquinolines are synthetic non-camptothecin analogs that poison hTop 1. Since the first indenoisoquinline, NSC 314622, was reported in 1978, many derivatives have been synthesized and tested for anticancer activity [186]. A Phase 1 clinical study of indotecan (LMP400) and indimitecan (LMP776) in adults with relapsed solid tumors and lymphomas was recently completed although study results have not been published [187].

c. Dibenzonaphthyridinones—ARC-111 was selected among dibenzonaphthyridinones for preclinical studies of its anticancer activity [181–183]. More recently, Genz-644282 has been the subject of both preclinical and clinical studies [188,189].

6. Mechanisms of type IIA topoisomerase poisoning and inhibition

The ability of type IIA topoisomerases to adopt a spectrum of conformational states is consistent with the notion that these enzymes must undergo extensive structural rearrangement during the course of strand passage (Fig. 2). In theory, modulating the activity of topoisomerases can be achieved by trapping them in any of these conformational states. However, two modes of action are utilized most successfully by type IIA topoisomerase inhibitors: (1) trapping of a cleavage complex by topoisomerase poisons or toxins and (2) inhibition of ATPase activity that leads to the blockage of enzyme turnover. Structural analyses of type IIA enzymes bound to topoisomerase poisons, toxins, or catalytic inhibitors have revealed their mechanisms of action. The mechanisms utilized by bacterial type IIA topoisomerase inhibitors may provide useful insights to the development of novel anticancer agents that target hTop 2.

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(1) Type IIA topoisomerase poisons

Several type IIA topoisomerase poisons are used successfully in the clinic as anticancer and antibacterial drugs (Fig. 3) [6, 24–31]. These drugs stabilize cleavage complexes that contain a DSB. Structural analysis of the catalytic core (the 55-kDa DNA breakage-reunion domain of the ParC subunit plus the 30-kDa Toprim domain of the ParE subunit) of *Streptococcus pneumoniae* Top 4 complexed with DNA and fluoroquinolones (including moxifloxacin, clinafloxacin, and levofloxacin) provided the first visualization of drug-stabilized type IIA topoisomerase cleavage complexes [33]. These structures, although determined at sub-optimal resolution (~4 Å), revealed that two fluoroquinolone molecules intercalated four-base pairs apart at the sites of strand breakage and are stacked against the flanking +1/+4 and −1/+5 base pairs [33]. The intercalated fluoroquinolone molecules physically prevent the 3′-OH from approaching the enzyme-linked 5′-phosphate and block religation of the broken DNA strands, which effectively trap cleavage complexes that contain a DSB. Thus, the strand breakage site-specific drug insertion provides a basis for topoisomerase poisoning by quinolones. In addition, the quinolone-stabilized cleavage complex is in a closed conformational state where the two halves of the cleaved DNA strands are tethered by base paring formed between the two cohesive ends [33]. Transition of a cleavage complex from a closed conformational state to an open conformational state is expected to be suppressed by the bound drug molecules; opening of the DNA-gate would disrupt the stacking between quinolone molecules and DNA bases, and expose the aromatic quinolone core to solvent. The interactions formed between amino acid residues and fluoroquinolone molecules in ternary complexes are not defined clearly because of the limited resolution. Nevertheless, the general vicinity of the quinolone-binding pocket matches with the quinolone resistance-determining region [190,191].

Although this initial set of structures of the quinolone-stabilized cleavage complex were determined at lower resolution [33], the key structural observations described above, including the intercalation of drug molecules at strand breakage sites and the cleavage complex being observed in the closed conformation, agree with subsequent high resolution structures [34,44,191–195]. A clearer picture of the exact mechanism of quinolone-topoisomerase interaction came from the higher resolution structures of the *Acinetobacter baumannii* Top 4 cleavage complexes stabilized by levofloxacin and moxifloxacin [34]. Importantly, the *A. baumannii* Top 4 structure revealed the chelation of a Mg^{2+} molecule by the *C*-3, *C*-4 diketo moiety of moxifloxacin (Fig. 3), an observation consistent with the involvement of Mg^{2+} in quinolone function [196,197]. Moreover, two conserved amino acid residues, Ser-84 and Glu88, located on helix α4 of the WHD domain form hydrogen bonds with the Mg^{2+}-coordinating water molecules. This Mg^{2+}-water bridge between the *C*-3, *C*-4 diketo moiety of floroquinolones and the conserved serine and glutamate/aspartate residues in the WHD domain of the GyrA/ParC subunit appears to be the only direct interaction between a fluoroquinolone and a topoisomerase [34,193]. Two conserved amino acid residues that correspond to Ser-83 and Asp-87 of *E. coli* GyrA are hot spots for quinolone-resistant mutations [26,198]. Thus, the presence of the Mg^{2+}-water bridge also provides the molecular basis for the quinolone resistance conferred by amino acid substitutions at these location [29,34].

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The crystal structures of drug-stabilized cleavage complexes of hTop 2α and hTop 2β showed that the Top 2-targeting anticancer drugs and the antibacterial quinolones most likely act in a similar manner [42,43]. The tetracyclic aglycone core of etoposide (Fig. 3), the tricyclic dihydroxy-anthraquinone moiety of mitoxantrone (Fig. 3), and the tricyclic acridine moiety of *m*-AMSA (Fig. 3) were observed to intercalate between the base pairs that flank the strand breakage sites, which prevents the religation of cleaved DNA strands. The interactions formed between the topoisomerase and each drug may explain the drug's specificity toward Top 2-mediated DNA breaks. Notably, a loop region and several residues involved in drug-binding were found to display extraordinary conformational flexibility, which reveals why the cleavage complexes formed with either hTop 2α or hTop 2β can be targeted by drugs with structurally distinct protein-interacting moieties (namely, the E-ring and glycosidic group of etoposide, the hydroxylalkylamino arms of mitoxantrone, and the methanesulfon-*m*-anisidide group of *m*-AMSA). The majority of the drug-interacting residues are conserved between hTop 2α and hTop 2β, consistent with the finding that both isoforms are the cellular targets of these drugs [24,25,27,28,30]. It is worth noting that the co-crystallization approach had been applied successfully to the structural analyses of etoposide- and mitoxantrone-bound cleavage complexes of hTop 2α [199], thus the obtained crystal structures of *m*-AMSA- and mitoxantrone-bound cleavage complexes of hTop 2β are expected to be functionally relevant. In contrast, the crystal structure of doxorubicin-bound cleavage complex was only determined using a post-crystallization drug-replacement procedure, and therefore the functional significance of this structure has remained to be elucidated [43].

To develop antibacterial drugs, it is preferable that one compound can target both DNA gyrase and Top 4. Dual targeting of DNA gyrase and Top 4 may increase the potency and reduce the appearance of drug resistance [200,201]. However, the accumulation of hTop 2β-induced DNA breaks are associated with deleterious chromosome translocation and rearrangement events, resulting in frequent occurrence of therapy-related leukemia [202,203]. Therefore, it would be clinically desirable to have an anticancer drug that preferentially targets hTop 2α. Structural studies revealed the presence of an hTop 2α-specific methionine residue that may be exploitable for this purpose [124,199]. Given the reactivity of methionine toward platinum(II) and the recent finding that the formation of a single coordination bond between methionine and platinum(II) can irreversibly trap the cleavage complexes formed by hTop 2α and 2β [199], the development of isoform-selective drug may be achieved by targeting this hTop 2α-specific methionine.

(2) NBTIs and allosteric modulators

In addition to type IIA topoisomerase poisons described in the previous section, new classes of small molecules with potent antibacterial activities have been identified as NBTIs in recent years [191,204–206]. GlaxoSmithKline has also reported a series of cyclohexyl-amides, amino-piperidines, and tricyclic compounds as NBTIs [206–210]. Among them, Gepotidacin (originally GSK2140944 [211,212]), an analog of GSK299423 (Fig. 3), and AZD0914 [213–215], an analog of quinoline pyrimidine trione-1 (QPT-1), are in clinical trials.

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Structures of GSK299423- and QPT-1-stabilized DNA gyrase cleavage complexes have been reported [191,192]. Two QPT-1 molecules bind to the same sites in the cleaved DNA as moxifloxacin in a ternary complex although the interaction of QPT-1 with DNA gyrase is completely different from that of moxifloxacin with DNA gyrase. As described in the previous section, fluoroquinolones interact with the conserved amino acid residues in the WHD domain of the GyrA/ParC subunit. In contrast, QPT-1 interacts with the conserved amino acid residues in the Toprim domain of the GyrB/ParE subunit [192], which may explain the activity of QPT-1 against fluoroquinolone-resistant strains of bacteria [216].

The GSK299423-stabilized, DNA gyrase cleavage complex has revealed a novel binding site utilized by this class of NBTI [191]. GSK299423 inserts its planar quinolone-carbonitrile moiety between the central (+2/+3 and +3/+2) base pairs enclosed by the strand breakage sites and the oxathiolo-pyridine group into a hydrophobic pocket formed by surrounding amino acid residues. It induces the formation of ternary complexes containing a single-strand DNA break, not a DSB [191]. Notably, this NBTI binding site falls on the dyad axis of the enzyme, suggesting that one type IIA topoisomerase-DNA complex can accommodate just one drug molecule (Fig. 4), in contrast to the binding of two drug molecules per cleavage complex for fluoroquinolones and QPT-1, as well as etoposide [192]. Upon the binding of an NBTI, the two cohesive DNA ends can no longer slide against one another. Thus, a single molecule can effectively lock the enzyme-DNA complex in its closed conformation [191]. As was the case with topoisomerase-fluoroquinolone-DNA ternary complexes [217], topoisomerase-NBTI-DNA ternary complexes could arrest replication fork progression *in vitro* [31].

A more recent work by GlaxoSmithKline has led to the discovery of thiophene antibacterials (Fig. 3) that are capable of inhibiting DNA gyrase via stabilization of the cleavage complex [218]. Co-crystallization of these novel inhibitors with DNA gyrase and DNA has revealed that this new class of compounds binds to a previously unrecognized pocket formed between the Toprim and WHD domains, away from the bound G-segment DNA which harbors the bindings sites of other Top 2 poisons described above. A major incentive for developing new compounds against bacterial type IIA topoisomerases is to overcome the growing resistance to quinolone antibacterial agents. In this regard, the development of NBTIs, including thiophene antibacterials, whose binding pockets are distinct and non-overlapping with the quinolones [218], may provide a new approach to conquering quinolone resistance and also inspire the discovery of novel hTop 2 poisons. Interestingly, the thiophene compound-bound structures of DNA gyrase-DNA complex were obtained in the presence of GSK945237 (Fig. 3), indicating that these two distinct classes of NBTIs target the same conformational state of the enzyme-DNA complex and may act synergistically [218].

(3) Toxins and regulatory proteins

The catalytic activities of type IIA topoisomerases are modulated through their interactions with various proteins. Several toxins and regulatory proteins that target DNA gyrase have been identified and characterized in bacteria [26,219,220]. An effective approach for blocking type IIA topoisomerase function is to prevent type IIA topoisomerases from

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binding to the G-segment DNA. Two types of proteins have been identified that act in this manner.

The pentapeptide repeat protein family has over 500 members [219,221]. Although the majority of them are found in bacteria, they are also found in *Arabidopsis*, zebrafish, mouse, and humans. MfpA and Qnr adopt a quadrilateral β-helix fold, with overall dimensions and distribution of negatively charged groups on their protein surface markedly resembling features of B-form DNA [222–225]. Biochemical and structural studies suggest that these DNA-mimicking proteins may interact with the primary DNA-binding groove of DNA gyrase (and perhaps Top 4), thereby blocking the binding of the G-segment (Fig. 4). Since the antibacterial activity of fluoroquinolones relies on the formation of gyrase-fluoroquinolone-DNA ternary complexes, the expression of either MfpA or Qnr antagonizes the actions of fluoroquinolones and, thus, may contributes to antibiotic resistance [220]. Despite the supposedly tight association between MfpA/Qnr and gyrase (K_d in the low μM to nM range), no structures of MfpA/Qnr-gyrase complexes are available. Therefore, it remains unclear how the binding specificity is defined to ensure the assembly of these inhibitory complexes *in vivo*, especially given the high local concentration of DNA and the presence of other DNA-mimicking proteins in cells. Identification of MfpB, a GTPase that modulates MfpA action and quinolone resistance [226], indicates that additional factors may regulate pentapeptide repeat protein function.

The chromosome-encoded and zinc-finger containing protein YacG is another bacterial type IIA topoisomerase regulator that inhibits DNA gyrase by interfering with the binding of the G-segment [227,228]. Rather than mimicking B-DNA and competing with the G-segment for the primary DNA binding groove of gyrase, a crystal structure of the YacG-DNA gyrase complex revealed that the zinc-finger of YacG interacts with the Toprim domain (Fig. 4) and protrudes into the G-segment-binding groove, thus occluding the binding of the G-segment [228]. Moreover, the C-terminal tail of YacG fits into a hydrophobic pocket on the surface of GyrB that is also targeted by the oxathiolo-pyridine group of NBTIs [191], which further stabilizes the inhibitory complex.

Simocyclinones, such as simocyclinone D8, are antibiotics that contain an aminocoumarin moiety [229,230]. The aminocoumarin antibiotics are known to be ATPase inhibitors of type IIA topoisomerases [26,27]. Although simocyclinone D8 can bind to the GyrB subunit of gyrase [231], it binds primarily to the GyrA subunit of gyrase (Fig. 4) [232–234]. As a result, this small molecule is capable of inhibiting the supercoiling activity of gyrase by preventing gyrase from binding to DNA, rather than by inhibiting the ATPase activity of gyrase [232]. Simocyclinone D8 also exhibits modest activities against Top 4 and hTop 2 [235–237].

Blocking the transportation of the T-segment by the F plasmid-encoded protein CcdB represents another mechanism of gyrase inhibition [238,239]. Structural studies indicated that CcdB binds to the large cavity enclosed by the two GyrA subunits by interacting with cavity-facing residues from the C-gate region of gyrase (Fig. 4) [240]. Since this cavity serves as a temporary storage for the T-segment DNA before its exit through the C-gate, the presence of CcdB would render gyrase inactive. Structural modeling further suggested that

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CcdB cannot be accommodated in the cavity if the cleavage complex adopts the closed conformation, a state essential for resealing the cleaved DNA [240]. Hence, CcdB-binding would promote the formation of a DSB [241].

(4) ATPase inhibitors

The transfer of the T-segment by a type II topoisomerase is driven by the conformational rearrangement of the GHKL ATPase domain in response to ATP binding and hydrolysis [121–123,127,128]. Therefore, inactivation of a type II topoisomerase can be achieved by restricting the nucleotide-dependent structural changes or inhibiting ATPase activity. Small molecules useful for both purposes have been identified [242,243]. The bisdioxopiperazines, such as ICRF-187 (dexrazoxane) (Fig. 3), inhibit eukaryotic Top 2 by arresting the two ATPase domains in the ATP-bound, dimerized form, effectively locking the entry gate in its closed state (Fig. 4) [244–247]. Since neither the G- nor T-segment is able to go through the entry gate in the presence of ICRF-187, this compound not only renders Top 2 inactive but also compromises the action of Top 2 poisons by suppressing the production of topoisomerase-induced DNA breaks [248]. Given that ICRF-187 on its own does not exhibit appreciable affinity toward the ATPase domain, it appears that the ATP-induced closure of the entry gate is required prior to the binding of ICRF-187. Indeed, structural analysis performed on the ATPase domain of yeast Top 2 revealed that a single ICRF-187 bound at the dimer interface without overlapping the ATP binding pockets [116]. Importantly, a glutamine residue that interacts with the γ-phosphate of ATP, and has been implicated in ATP hydrolysis, also forms hydrogen bonds with ICRF-187. This observation suggests that ICRF-187 may restrict the movement of residues involved in ATP hydrolysis and explains the compound's ability to inhibit ATPase activity. Interestingly, while the closed entry gate is structurally two-fold symmetric, ICRF-187 (Fig. 3) is an asymmetric molecule with only one methyl group present in the 2-carbon linker that connects the two piperazinedione moieties [242,243]. As a result, only one of the methyl group interacting surfaces in the binding pocket is exploited. In contrast, ICRF-193, the most potent bisdioxopiperazine, contains two methyl groups and, thus, binds tighter to eukaryotic Top 2s [249].

Unlike bisdioxopiperazine compounds that act as uncompetitive inhibitors, the aminocoumarin antibiotic novobiocin (Fig. 3) is a competitive inhibitor of the ATPase activity of bacterial type IIA topoisomerases [250,251]. Structural studies established that the sugar and coumarin moieties of novobiocin compete with ATP for the nucleoside binding site [252–254]. However, rather than occupying the triphosphate binding site, the benzoyl moiety of novobiocin extends toward the opposite direction without contacting the neighboring subunit and, thus, would not induce closure of the entry gate like ATP does [252,255]. It appears that eukaryotic type IIA topoisomerases are not targeted by novobiocin due to divergent evolution of drug-binding residues. It has been shown that the efficacy of novobiocin can be significantly reduced by the occurrence of a single amino acid substitution in the drug-binding pocket [256,257]. Unexpectedly, anticancer activity of novobiocin has been reported, likely achieved via targeting Hsp90 [258–261]. Since Hsp90 also harbors a GHKL ATPase domain, whose structure is very similar to that of GyrB [106,262], this finding suggests that novobiocin may have a broader target specificity than previously realized.

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7. hTop 2-targetting anticancer drugs

As listed below, hTop 2 poisons are successful anticancer drugs used in the treatments of various cancers. However, two serious side effects, therapy-related cancer [203,263–266] and cardiotoxicity [267–270], associated with these drugs limit their use. Etoposide (Fig. 3) and other hTop 2 poisons cause the development of secondary malignancies, especially therapy-related acute myeloid leukemia (t-AML) [271,272] and therapy-related acute promyelocytic leukemia (t-APL) [273–276]. t-AML is caused by hTop 2-mediated, and more specifically hTop 2β-mediated [201], DSBs and chromosome rearrangements in the mixed lineage leukemia (MLL) gene [277–281], and t-APL is caused by the translocation between the promyelocytic leukemia (PML) gene and the retinoic receptor α gene [273–275].

Doxorubicin (Fig. 3) is a potent anticancer drug that can be used to treat many cancers. However, its full potential has not been realized due to the cardiotoxicity associated with its use [267–270]. The primary mechanism of doxorubicin-associated cardiotoxicity appears to be oxidative stress, due to increased levels of reactive oxygen species (ROS) and lipid peroxidation [282–285]. The main pathway for ROS formation by anthracyclines is the formation of semiquinone radicals resulting in redox cycling [283,285]. Another source of ROS generated by anthracyclines results from formation of doxorubicin-iron complexes that catalyze the Fenton reaction [286–288]. Cardiomyocytes are particularly sensitive to oxidative stress. hTop 2β is the only topoisomerase expressed in myocytes [289,290] and its poisoning by doxorubicin, in addition to increased ROS, may contribute to the cardiotoxicity of doxorubicin [291,292]. Further studies are required to determine the exact mechanism(s) of the cardiotoxicity of doxorubicin but the current strategy to prevent cardiotoxicity is to limit the cumulative dose of doxorubicin.

In addition to these side effects, P-glycoprotein (multidrug resistance protein 1) confers resistance to epipodophyllotoxins and anthracyclines [293,294]. Despite the clinical issues described above, hTop 2 poisons are among the most widely prescribed anticancer drugs. Some Top 2 poisons currently used in the clinic are described below.

(1) hTop 2 poisons

a. Epipodophyllotoxins – Etoposide and Teniposide—Podophyllotoxin was originally isolated from the podophyllum plants, American *Podophyllum peltatum* and *Podophyllum emodi* [295]. Easily accessible podophyllotoxin is used in the synthesis of etoposide (Etopophos, VePesid, VP-16) and teniposide (Vumon, VM-26) [296]. Etoposide (Fig. 3) is widely used in the treatments of solid tumors, such as testicular cancer and small cell lung cancer [297]. It is also used to treat lymphomas and nonlymphocytic leukemia. To improve its water solubility, a prodrug etoposide phosphate (Etophos) was developed for intravenous use [298,299]. Teniposide is an analog of etoposide and is approved for the treatment of acute lymphoblastic leukemia (ALL) in children [300]. It is also used to treat other cancers, including Hodgkin's lymphoma and some brain cancers. Teniposide is less water soluble and has higher plasma protein binding than etoposide [301,302].

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b. Anthracyclines – Doxorubicin, Daunorubicin, and Epirubicin—Doxorubicin (Adriamycin, Doxil) (Fig. 3) is an anthracycline antibiotic originally isolated from *Streptomyces peucetius* [303,304]. It is used to treat a wide variety of cancers, including ALL, acute myeloblastic leukemia (AML), breast carcinoma, ovarian carcinoma, Kaposi's sarcoma, Wilms' tumor, thyroid carcinoma, gastric carcinoma, and Hodgkin's disease [305,306]. Doxil is a form of doxorubicin contained inside a liposome (liposomal doxorubicin) for a slow release to treat AIDS-related Kaposi's sarcoma, multiple myeloma, and ovarian cancer [306–311]. Doxorubicin is one of the most potent anticancer drugs but its use is limited by the cumulative dose-dependent cardiotoxicity [267–270].

Daunorubicin (Cerubidine, DaunoXome) (Fig. 3) has similar therapeutic effects to doxorubicin [312,313]. It is used to treat ALL, AML, chronic myelogenous leukemia (CML), and Kaposi's sarcoma [314–317]. DaunoXome is liposomal daunorubicin that is used for the treatment of AIDS-related Kaposi's sarcoma [315,318].

Epirubicin (Ellence) is an active isomer of doxorubicin [319]. Although epirubicin has similar therapeutic effect to doxorubicin, epirubicin is preferred over doxorubicin in certain chemotherapy regimens because it has fewer side effects [320,321]. Epirubicin is eliminated faster and has reduced toxicity compared to doxorubicin. The spatial orientation of the hydroxyl group at the 4' carbon of the sugar moiety differs in doxorubicin and epirubicin. Epirubicin's 4' hydroxyl is in an equatorial position allowing for rapid conjugation of epirubicin with glucuronic acid, which could account for its faster elimination and lower toxicity [322,323]. Liposomal epirubicin has shown to be an effective agent to treat brain glioma [324,325].

Anthracyclines act as Top 2 poisons. In addition, they can intercalate into DNA [326] and may influence the functions of various proteins besides hTop 2 [327–329]. As previously described, anthracyclines also generate ROS [283,285–288].

c. Mitoxantrone—Mitoxantrone (Novantrone) is a synthetic anthracenedione (Fig. 3) developed as an alternative to anthracyclines to reduce cardiotoxicity while retaining antineoplastic activity [330,331]. It is used for the treatment of multiple sclerosis and AML [332–334]. While mitoxantrone has higher tolerability than the anthracyclines, cardiomyopathy is still a concern in long-term treatment [331,335,336].

(2) hTop 2 catalytic inhibitor

a. Dexrazoxane—Dexrazoxane (Zinecard, Cardioxane, ICRF-187) is a bisdioxopiperazine (Fig. 3) and is a derivative of ethylenediaminetetraacetic acid [242]. Dexrazoxane is the only drug approved to treat cardiotoxicity caused by anthracyclines [337–339]. Its cardioprotective mechanism is attributed to the chelation of iron by dexrazoxane, thus decreasing the production of ROS during anthracycline treatment [340,341]. Dexrazoxane is orally active as a prodrug that is hydrolyzed, by sequential ring openings, into the active metabolite ADR-925 [340,342,343]. Recent studies have indicated that dexrazoxane's cardioprotective effect may be associated with catalytic inhibition of hTop 2 [290,344].

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8. Prospective

Both hTop 1 and hTop 2s are targets of current anticancer drugs. New inhibitors of these enzymes are also in the pipeline. Thus, topoisomerases continue to be important therapeutic targets of anticancer drugs.

Clinically used Top 2-targetting drugs act on both hTop 2α and hTop 2β. The expression of hTop 2α is often elevated in cancer cells and the anticancer activity of these drugs is mainly mediated by the poisoning of hTop 2α. Furthermore, a significant number of studies suggest that both the development of therapy-related leukemia and cardiotoxicity are caused by the poisoning of hTop 2β. Thus, it seems reasonable to develop hTop 2α-specific poisons as anticancer drugs to prevent the therapy-related leukemia and cardiotoxicity. The development of either isoform-specific hTop 2 poisons or potent hTop 2 catalytic inhibitors may provide safer therapeutic options for cancer patients.

In contrast to topoisomerase poisons, topoisomerase catalytic inhibitors have not been successfully used in clinic. Despite the lack of structural similarities between hTop 1, a type IB topoisomerase, and hTop 2s, type IIA topoisomerases, some small molecules, including our novel quinolones, have been shown to act as dual catalytic inhibitors of hTop 1 and hTop 2s. Thus, catalytic inhibitors of multiple topoisomerases may become successful anticancer drugs.

Human cells also contain two type IA topoisomerases, hTop 3α and hTop 3β. Although some small molecules that inhibit bacterial type IA topoisomerases have been identified only in recent years, hTop 3 inhibitors may be discovered and developed as new anticancer drugs in the future.

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Abbreviations:

ALL	acute lymphoblastic leukemia
AML	acute myeloblastic leukemia
CML	chronic myelogenous leukemia
DSB	double-strand break
G	Gate
h	human
m	mitochondria
MLL	mixed lineage leukemia

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NBTI	new bacterial topoisomerase inhibitor
PML	promyelocytic leukemia
QPT-1	quinoline pyrimidine trione-1
ROS	reactive oxygen species
Top 1	topoisomerase I
Top 3	topoisomerase III
Top 4	topoisomerase IV
t-AML	therapy-related acute myeloid leukemia
t-APL	therapy-related acute promyelocytic leukemia
T	Transfer

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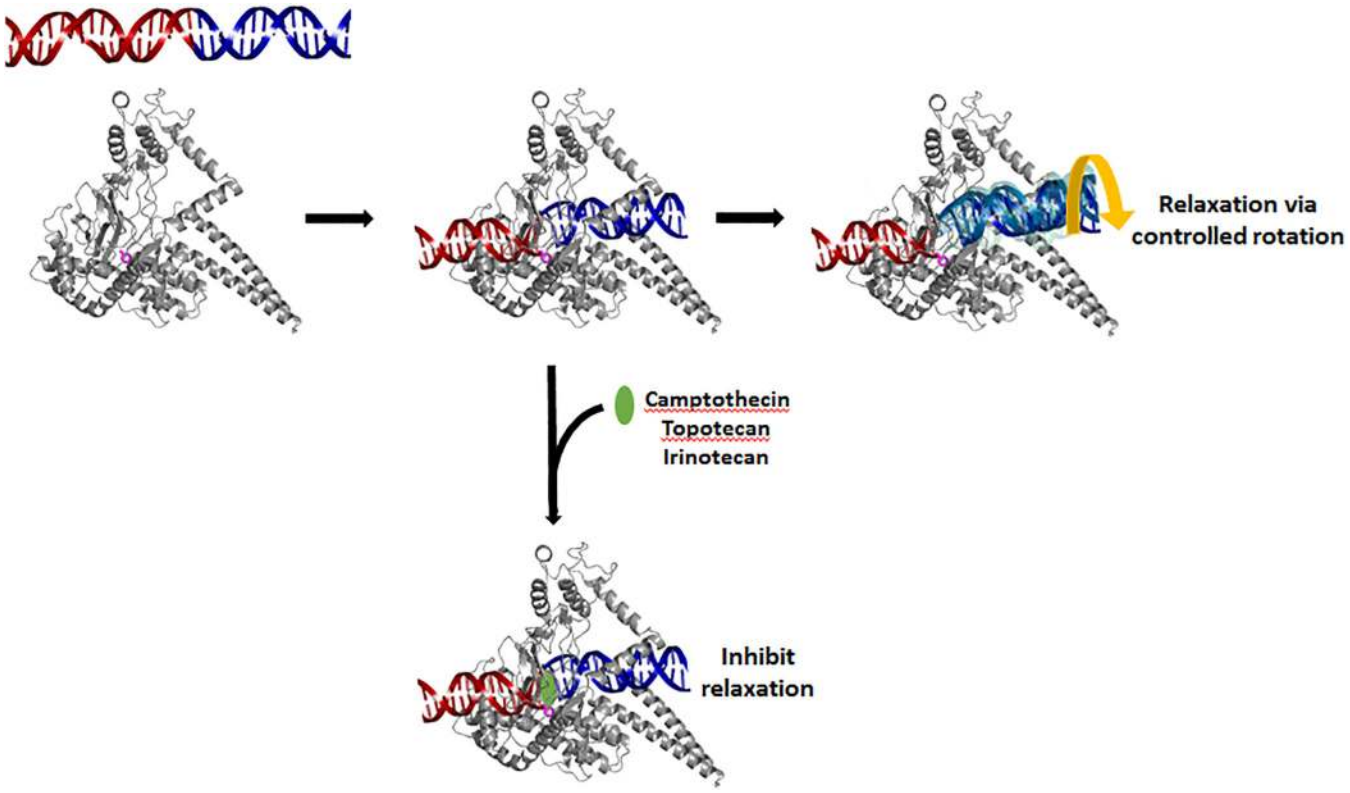

Figure 1. Relaxation reaction catalyzed by hTop 1 and the effect of camptothecin class of anticancer agents.

Type IB topoisomerases cleave one strand of supercoiled DNA via the formation of a protein-linked phosphotyrosyl bond between the catalytic tyrosine (purple sticks) and the 3′-phosphate group. While the DNA duplex upstream of the break (red) is bound tightly by hTop 1, very few interactions are present between the downstream DNA duplex (blue) and the enzyme, which allows both positive and negative superhelical tension in DNA to be released by the rotation of downstream DNA duplex about the break. The insertion of camptothecin class of anticancer agents (green ellipsoid) stabilizes the hTop 1-mediated DNA strand break and inhibits the enzyme's relaxation activity. The cartoon representation of hTop 1 (PDBid: 1RRJ [137]) was generated using PyMol (http://pymol.org).

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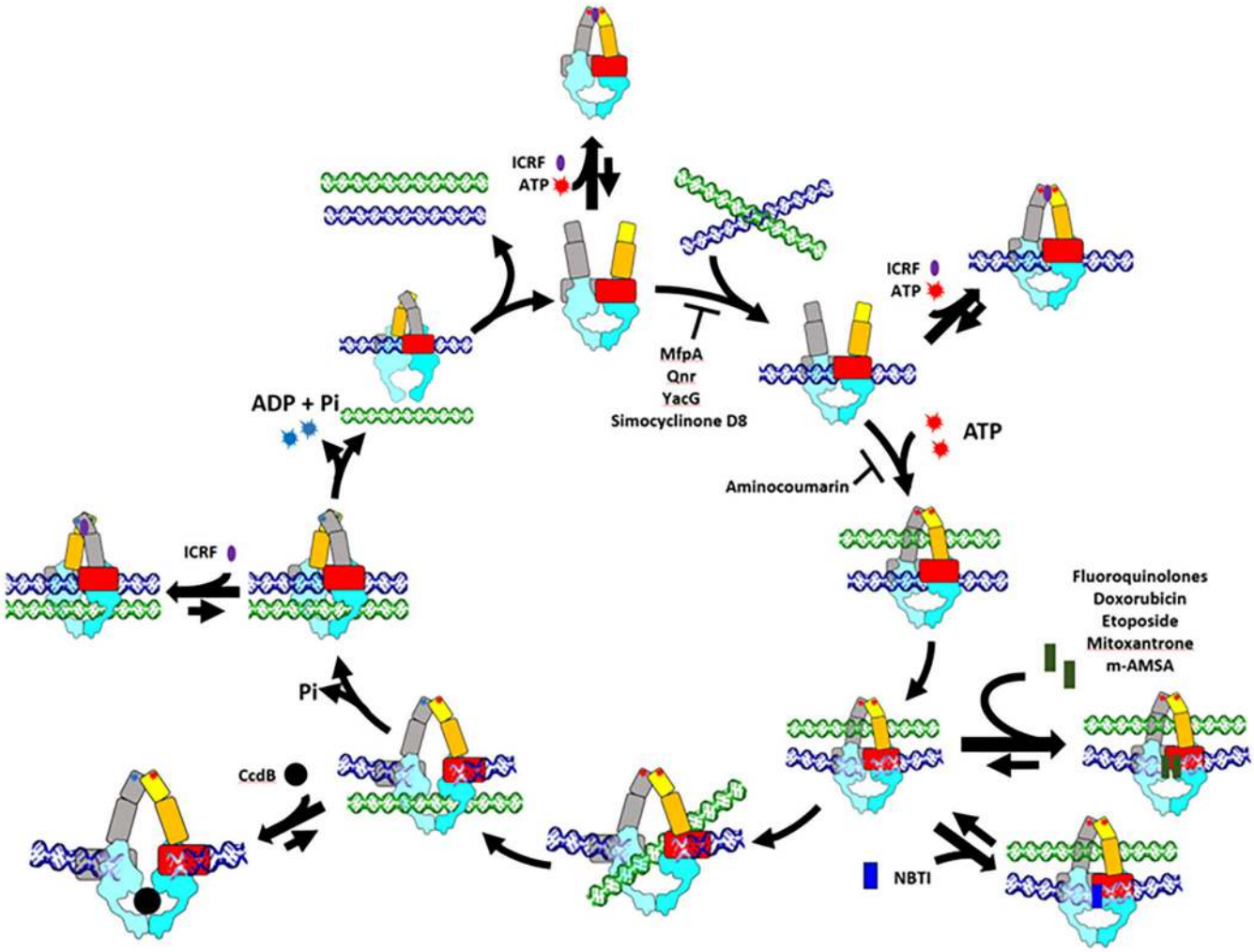

Figure 2. Catalytic cycle and inhibitors of type IIA topoisomerases.

The catalytic cycle of type IIA topoisomerases starts from the entry of G-segment DNA (blue) through an opened N-gate. Binding of two ATP molecules induces closure of the N-gate to facilitate the capture of T-segment DNA (green). The Cleavage of the G-segment followed by pulling the broken DNA ends apart creates a path that allows the T-segment to go through. This duplex passage event is likely driven by the hydrolysis of one ATP and a clockwise rotation of the N-gate, which not only pushes the T-segment through the DNA-gate but also causes the upper cavity enclosed by the N-gate to collapse to prevent the T-segment from moving backward. The religation of the cleaved G-segment is expected to shrink the bottom cavity and thus induces opening of the C-terminal exit gate and the release of the T-segment. The second ATP hydrolysis event then takes place to reset the enzyme for next catalytic cycle. The turnover of type IIA topoisomerases may be blocked by arresting the enzyme at different intermediate states upon the binding of small molecule inhibitors or regulatory proteins. The ATPase, transducer, Toprim, and the remaining C-terminal fragment (from WHD to C-gate) are in yellow, orange, red, and cyan, respectively. The domains of the second protomer are colored grey and light blue. The design of this figure was inspired by Larsen et al. [345].

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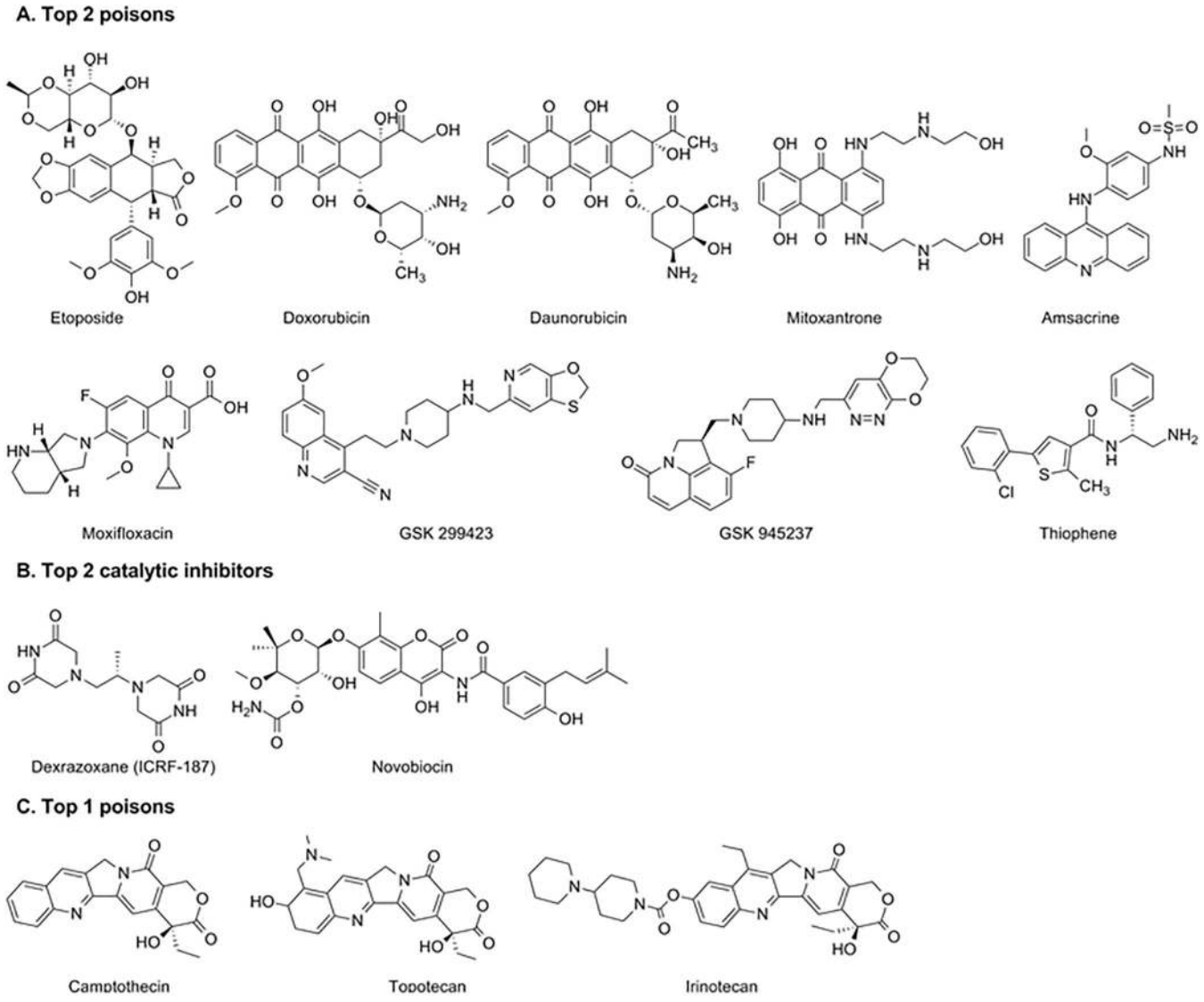

Figure 3. Structures of topoisomerase inhibitors.

A. Type IIA topoisomerase (Top 2) poisons. B. Type IIA topoisomerase (Top 2) catalytic inhibitors. C. Type IB topoisomerase (Top 1) poisons.

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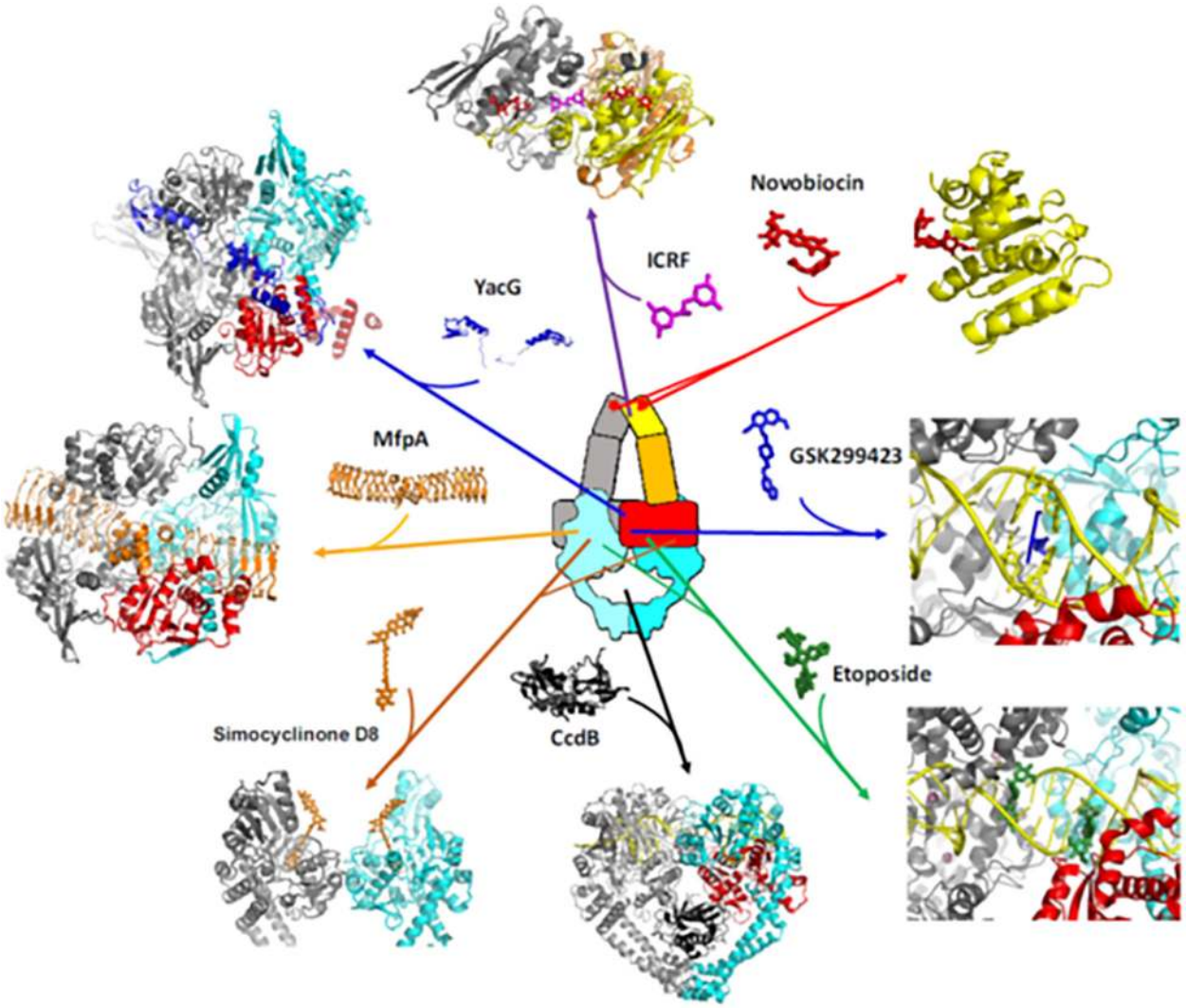

Figure 4. Targeting sites and binding modes of selected type IIA topoisomerase inhibitors and regulatory proteins.

Functional modulation of type IIA topoisomerases can be achieved by the binding of small molecules and regulatory proteins to various sites in the enzyme. The crystal structures of type IIA topoisomerases in complexes with small molecules {ICRF-187 (PDBid: 1QZR [117]), novobiocin (PDBid: 4URO [346]), GSK299423 (PDBid: 2XCS [191]), etoposide (PDBid: 3QX3 [42]), simocyclinone D8 (PDBid: 2Y3P [233])} and regulatory proteins {YacG (PDBid: 4TMA [228]), CcdB toxin (PDBid: 1X75 [240])} were generated using PyMol (http://pymol.org). The structural model of MfpA-bound GyrA was constructed by manual docking of the MfpA (PDBid: 2BM4 [222]) to the N-terminal fragment of GyrA (PDBid: 1AB4 [107]) followed by stereochemical idealization.