Chelators at the Cancer Coalface: Desferrioxamine to Triapine and Beyond
Yu Yu, Jacky Wong, David B. Lovejoy, Danuta S. Kalinowski, and Des R. Richardson

Abstract The importance of iron and copper in cancer biology has been well established. Iron plays a fundamental role in cellular proliferation and copper has been shown to be a significant cofactor for angiogenesis. Early observations with the chelator used for the treatment of iron overload, desferrioxamine, showed that it had promise as an anticancer agent. These results sparked great interest in the possibility of developing more effective iron chelators for cancer therapy. The recent entry into clinical trials of the iron-binding drug, Triapine, provides evidence of the potential of this antimetastasis strategy. Likewise, chelators originally designed to treat disorders of copper overload, such as penicillamine, trientine, and tetrathiomolybdate, have also emerged as potential anticancer drugs, as they are able to target the key angiogenic cofactor, copper. In this review, we will discuss the development of these and other chelators that show potential as anticancer agents.

Iron (Fe) and copper (Cu) are fundamental for life (1, 2). The presence of Fe in ribonucleotide reductase is vital for proliferation owing to its role in catalyzing the rate-limiting step of DNA synthesis (i.e., the conversion of ribonucleotides into deoxyribonucleotides; review ref. 1). Ultimately, the importance of Fe is highlighted by the fact that Fe deprivation leads to G1-S arrest and apoptosis (1). Neoplastic cells, in particular, have a high Fe requirement due to their rapid proliferation (1). To attain more Fe, neoplastic cells express higher levels of the transferrin receptor 1 (TfR1) and take up Fe at a greater rate than their normal counterparts (1). This is reflected by the ability of tumors to be radiolocalized using $^{67}$Ga, which binds to the Fe transport protein, transferrin, for delivery via TfR1 (3, 4). Similarly, phosphorothiolated antisense TfR1 oligonucleotides targeted to TfR1 mRNA showed selective anticancer activity (5), confirming the importance of Fe in cancer cell growth. These observations show how Fe chelation may be a suitable therapeutic strategy for cancer treatment.

In addition to Fe, Cu is also a promising therapeutic target due to its key role in angiogenesis (6). Chelation of Cu suppresses several angiogenic mediators, including vascular endothelial growth factor-1, fibroblast growth factor-1, interleukin (IL)-1, IL-6, IL-8, and nuclear factor-$
\text{kappa}B$ (7). Because angiogenesis is critical for tumor metastasis (6), the ability of Cu chelators to inhibit angiogenesis represents a novel therapeutic strategy for cancer chemotherapy. This is confirmed by the recent entry into clinical trials of the Cu chelator tetrathiomolybdate (6).

Iron and Copper Metabolism

Iron transport into cells occurs by the binding of diferric transferrin to the TfR1 followed by receptor-mediated endocytosis (review ref. 8; Fig. 1). The subsequent release of Fe from transferrin occurs by a decrease of endosomal pH to 5.5 (8). The divalent metal transporter 1, an endosomal membrane protein, is then responsible for transporting free Fe out of the vesicle (Fig. 1; ref. 9). Once transported into the cytoplasm, Fe enters the putative labile Fe pool where it may be distributed to heme-containing proteins; non-heme-containing proteins, such as ribonucleotide reductase; or stored in the Fe storage protein, ferritin (Fig. 1; ref. 8). Intracellular Fe can be released via the ferroportin 1 transporter (10). Iron efflux is a particularly important function of enterocytes, hepatocytes, and macrophages, which are involved in Fe absorption, metabolism, and recycling, respectively (8). This process is linked with the ferroxidase activity of the Cu-containing proteins ceruloplasmin and hephaestin (11). Thus, Fe and Cu metabolism are associated.

The mechanism of Cu transport into human cells involves the high-affinity Cu transporter-1 (Fig. 1). The ATPase enzymes ATP7A and ATP7B, which are mutated in Menke’s and Wilson’s disease, respectively, are involved in Cu efflux and metabolism (Fig. 1; ref. 2). Extracellular Cu exists as Cu(II) and is reduced to Cu(I) before being transported into cells by the high-affinity Cu transporter-1 (2). A membrane-bound reductase is responsible for Cu(II) reduction (2). Upon entering cells, Cu binds to...
reduced glutathione and HAH1 (also known as ATX1 antioxidant protein 1 homologue ATOX1) that act as Cu chaperones to distribute Cu to proteins including metallothionein, ceruloplasmin, and hemocyanin (2).

The essential roles of Fe and Cu in key metabolic processes suggest that these nutrients are targets for anticancer therapy. However, the potential of these strategies has only recently been systematically explored.
Iron and Cancer Therapy: Desferrioxamine as an Anticancer Agent

The Fe chelator desferrioxamine (Fig. 2) is used clinically for the treatment of Fe-overload disorders (12, 13). Desferrioxamine was the first commercially available Fe chelator to be assessed in cancer therapy, where, for example, it was shown to reduce bone marrow infiltration of tumor cells in seven of nine neuroblastoma patients (Table 1; ref. 12).

Although desferrioxamine has some antiproliferative activity, it suffers serious limitations (13). It is highly hydrophilic, orally inactive, has poor membrane permeability, and is expensive to produce (13). It also possesses a short plasma half-life due to rapid metabolism (13). These limitations indicate why desferrioxamine failed to show anticancer activity in some studies (14, 15). Indeed, the failure of this drug in several clinical trials relates to the fact that it was never designed for cancer treatment, its purpose being as a therapeutic for Fe overload. As a result of the limited success of desferrioxamine, more effective Fe-binding ligands have been designed with a particular emphasis on chelator lipophilicity and membrane permeability. These are discussed below.

New-Generation Lipophilic Fe Chelators

Triapine. Triapine (3-aminopyridine-2-carboxaldehyde thiosemicarbazone; 3-AP; Fig. 2) is a tridentate chelator that ligates Fe via a sulfur and two nitrogen donor atoms (16). Triapine has been suggested to be one of the most potent inhibitors of ribonucleotide reductase yet identified (17). Human ribonucleotide reductase is a tetramer of two nonidentical homodimers, R1 and either R2 or p53R2 (18). R2 is involved in DNA synthesis for housekeeping, whereas p53R2 is a p53-targeted gene that is transactivated by DNA damage (19). Similar to R2, p53R2 possesses an Fe-binding site important for enzymatic function (18). Triapine can equally inhibit both R2 and p53R2, whereas the clinically used ribonucleotide reductase inhibitor, hydroxyurea, was relatively ineffective at inhibiting ribonucleotide reductase activity of the p53R2 subunit (18).

A recent study reported that the Triapine-Fe(II) complex was significantly more active at inhibiting ribonucleotide reductase than free Triapine (20). Triapine did not remove Fe from the active site of R2 or p53R2. Instead, this chelator formed a complex with Fe(III), which was reduced to Fe(II) that generated reactive oxygen species and quenched the ribonucleotide reductase tyrosyl radical (20). This inactivated the enzyme and prevented DNA repair and synthesis (20). These results were consistent with prior observations by our laboratory showing that the Triapine-Fe complex was redox active (21).

Building on the idea that a ribonucleotide reductase inhibitor may act as a radiosensitizer due to inhibition of DNA repair, Triapine has been examined in conjunction with radiotherapy (22). In mice bearing a U251 glioma or PSN1 pancreatic carcinoma, radiotherapy followed by Triapine was the most effective combination at inhibiting tumor growth (22).

Triapine is one of the most comprehensively assessed Fe chelators with antitumor activity. A number of phase I clinical trials have been reported and are summarized in Table 1. The most recent trial as a single agent showed that Triapine decreased serum tumor markers associated with stable disease in 4 of 21 patients (Table 1; ref. 17). At a dose of 120 mg/m²/d every 2 weeks, Triapine was well tolerated, whereas a dose of 160 mg/m²/d resulted in dose-limiting toxicities in three of six patients (17). The hematologic toxicities were anemia, thrombocytopenia, leucopenia, and met-hemoglobinemia (17). Glucose-6-phosphate dehydrogenase deficiency in patients has been reported to cause Triapine treatment complications (23). Patients carrying glucose-6-phosphate dehydrogenase deficiency developed severe met-hemoglobinemia and hemolysis upon treatment (23). This observation may be linked to Triapine redox activity (23) and the inability of patients with glucose-6-phosphate dehydrogenase deficiency to effectively reduce methemoglobin to its ferrous state (23).
### Table 1. Summary of clinical trials with the Fe chelators, desferrioxamine and Triapine, and Cu chelators, tetrathiomolybdate and d-penicillamine

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. patients</th>
<th>Outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFO</td>
<td>9 patients with neuroblastoma</td>
<td>7 patients showed decrease in bone marrow infiltration; 1 patient showed a 50% reduction in tumor mass</td>
<td>12</td>
</tr>
<tr>
<td>DFO</td>
<td>10 children with recurrent neuroblastoma</td>
<td>No partial or complete responses, although decreased serum ferritin were noted in 4 patients</td>
<td>14</td>
</tr>
<tr>
<td>DFO</td>
<td>14 patients with advanced hormone-refractory prostate cancer</td>
<td>13 patients had disease progression, although 9 had stable measurable or evaluable disease</td>
<td>62</td>
</tr>
<tr>
<td>DFO</td>
<td>23 patients with advanced neuroblastoma and 2 patients with PNET</td>
<td>In previously untreated patients, there were 15 complete responses and 2 partial responses. In patients who had a different drug regimen previously, there were 2 very good partial responses and 4 partial responses. Median survival for most patients was 22 mo</td>
<td>63</td>
</tr>
<tr>
<td>DFO</td>
<td>57 patients with advanced neuroblastoma</td>
<td>Following four treatment courses, almost all patients underwent surgery. After surgery, there were 24 complete responses, 26 partial responses, 3 minor responses and 4 with disease progression</td>
<td>64</td>
</tr>
<tr>
<td>DFO IFNα (Roferon)</td>
<td>7 patients with inoperable hepatocellular carcinoma</td>
<td>Compared with 5 untreated patients, the treated patients had a longer survival rate, increased tumor regression and less progressive disease</td>
<td>65</td>
</tr>
<tr>
<td>DFO</td>
<td>9 patients with refractory malignant disease</td>
<td>Partial responses were observed in 2 of 4 patients with refractory non–Hodgkin’s lymphoma</td>
<td>66</td>
</tr>
<tr>
<td>Triapine</td>
<td>27 patients with advanced cancer</td>
<td>8 patients experienced stabilization of disease for 2-4 mo, the remaining patients experienced progression. No objective tumor responses were observed</td>
<td>67</td>
</tr>
<tr>
<td>Triapine</td>
<td>24 patients with refractory leukemia</td>
<td>No patient had an objective response. Over 70% patients had &gt;50% reduction of WBC count</td>
<td>68</td>
</tr>
<tr>
<td>Triapine</td>
<td>32 patients with different tumor types</td>
<td>No partial or complete responses were observed; 5 patients showed a positive antitumor effect, in which 2 achieved disease stabilization; 4 of the 5 patients had metastatic disease</td>
<td>69</td>
</tr>
<tr>
<td>Triapine</td>
<td>26 patients with progressive metastatic or locally advanced cancer</td>
<td>3 patients had objective responses; 2 other patients achieved a partial response; another patient achieved tumor size reduction without meeting the criteria for a partial response</td>
<td>25</td>
</tr>
<tr>
<td>Triapine</td>
<td>21 patients with advanced or metastatic cancer</td>
<td>No partial or complete responses of tumor size reduction were observed; 2 patients remained progression-free for 6 and 10 mo, whereas 4 others achieved stable disease for 3-4 mo</td>
<td>17</td>
</tr>
<tr>
<td>Triapine</td>
<td>31 patients with refractory acute leukemia and high-risk MDS</td>
<td>4 patients achieved a complete response after the first cycle of therapy</td>
<td>24</td>
</tr>
<tr>
<td>Tetrathiomolybdate</td>
<td>18 patients with metastatic cancer (14 evaluable for response)</td>
<td>Progression or stable disease for &lt;90 d in 8 of 14 patients. In the remaining 6 patients, there was stable disease (5/6) or progression at one site (stable elsewhere; 1/6)</td>
<td>61</td>
</tr>
<tr>
<td>Tetrathiomolybdate</td>
<td>15 patients with advanced kidney cancer (13 evaluable for response)</td>
<td>Disease progression before 12 wk in 5 patients, disease progression at 12 wk in 4 patients, disease progression at 28-45 wk in 4 patients</td>
<td>51</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>40 patients with newly diagnosed glioblastoma multiforme</td>
<td>Median survival of 11.3 mo and progression-free survival of 7.1 mo (no significant difference to reference group), Penicillamine did not improve survival in these patients</td>
<td>54</td>
</tr>
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Abbreviations: DFO, desferrioxamine; ara-C, 1-β-D-arabinofuranosylcytosine; CHOP, cyclophosphamide-Adriamycin-vincristine-prednisone; PNET, primitive neuroectodermal tumors; MDS, myelodysplastic syndrome; D-CECaT, deferoxamine, cyclophosphamide, etoposide, carboplatin, and thiotepa.
The effect of combining Triapine with cytarabine (24) and gemcitabine (25) have also been investigated (Table 1). These trials showed a number of positive results; in particular, the study with gemcitabine resulted in some objective responses. Triapine is currently in phase II clinical trials in combination with a range of chemotherapeutics. Considering these results, Triapine may become the first Fe chelator to be widely used as an anticancer drug.

Pyridoxal isonicotinoyl hydrazone analogues. Pyridoxal isonicotinoyl hydrazone is a tridentate ligand that was first reported as a biologically effective Fe chelator by Ponka et al. (26). Major advantages of this chelator relative to deferoxamine include oral availability, high membrane permeability, and simple synthesis (16, 27). Studies of the structure-activity relationships of pyridoxal isonicotinoyl hydrazone analogues identified 2-hydroxy-1-naphthylaldehyde isonicotinoyl hydrazone (311) as one of the most active ligands (28). Subsequent studies with 311 found that it inhibits growth of many human cancer cells (29). The ability of 311 to mobilize Fe results in the depletion of Fe pools necessary for ribonucleotide reductase activity, leading to apoptosis (27, 29). Indeed, electron paramagnetic resonance studies showed that 311 decreased the ribonucleotide reductase tyrosyl radical that leads to inhibition of this enzyme (29).

Apart from the activity of chelators at inhibiting ribonucleotide reductase, several studies have shown that their effect on the expression of molecules involved in cell cycle control could be a factor in their antitumor activity. For instance, deferoxamine and 311 decreased levels of the cell cycle regulators cyclins D1, D2, and D3 (30). These proteins bind with cyclin-dependent kinase 4 to form a catalytically active dimer that phosphorylates the retinoblastoma protein, which is necessary for cell cycle progression (30). Additionally, 311 reduced expression of cyclin-dependent kinase 2 and the cyclins A and B1 (30). Inhibition of expression of these molecules would be effective in inducing cell cycle arrest. This activity was not observed after incubation of cells with the Fe complexes of deferoxamine or 311, or the ribonucleotide reductase inhibitor hydroxyurea (30).

The significantly greater antitumor activity of 311 and the success of Triapine led to studies assessing the structure-activity relationships of several new series of aroylhydrazone/thiosemicarbazone hybrid ligands. These included the 2-hydroxy-1-naphthylaldehyde isonicotinoyl hydrazone series (31), di-2-pyridylketone isonicotinoyl hydrazone series (32), and, more recently, the di-2-pyridylketonethiosemicarbazone series (33). The latter compounds showed the greatest antican cer activity and are described below.

**Di-2-pyridylketone thiosemicarbazone series of chelators.** Of the di-2-pyridylketone thiosemicarbazone chelators, the analogue di-2-pyridylketone-4,4′,dimethyl-3-thiosemicarbazone (Dp44mT; Fig. 2) was the most active against neoplastic cell lines (34). In fact, over 28 cell types, the average IC$_{50}$ was 0.03 ± 0.01 μmol/L, being significantly more effective than the established cytotoxic agent, doxorubicin (IC$_{50}$ = 0.62 ± 0.35 μmol/L; ref. 34). Moreover, Dp44mT showed selective activity against tumor cells compared with normal cells such as fibroblasts, where the IC$_{50}$ was >25 μmol/L (33). Dp44mT has high Fe chelation efficacy, with its ability to inhibit Fe uptake from transferrin and increase Fe release from cells being greater than deferoxamine and similar to 311 (33). The Dp44mT-Fe complex was also capable of inducing intracellular reactive oxygen species, which probably plays a role in its antitumor activity (33). Importantly, the antiproliferative activity of Dp44mT was not affected by p53 status (34). This serves as a therapeutic advantage, as >50% of tumors contain functionally defective p53, which inhibits apoptosis induction by chemotherapeutics (34). Studies examining the mechanism of action of Dp44mT showed that it caused apoptosis (33) and overcomes resistance to established cytotoxics (34).

*In vivo* studies in mice showed that Dp44mT, administered at 0.4 mg/kg twice daily, reduced M109 lung carcinoma growth to 47% of the control after 5 days of treatment (33). A subsequent investigation in nude mice with human melanoma xenografts showed that Dp44mT (0.4 mg/kg/d) over 7 weeks decreased tumor growth to 8% of the control. At this dose, Dp44mT was well tolerated with no hematologic or biochemical abnormalities (34). However, fibrotic myocardial lesions were identified at the higher dose of 0.75 mg/kg and to a lesser extent at 0.4 mg/kg. This effect may be due to the marked reduct activity of the Dp44mT-Fe complex (33, 35) and suggests that further optimization of the dose and mode of administration is necessary (34).

Dp44mT and other Fe chelators, including 311 and deferoxamine, markedly up-regulate the expression of the metastasis suppressor gene N-myc downstream regulated gene-1 (Ndrg1) in tumor cells *in vitro* (36) and *in vivo* (34). Increased Ndrg1 expression was correlated to chelator antiproliferative activity and was reversed by Fe repletion (36). The fact that Fe deprivation leads to up-regulation of this metastasis suppressor suggests another link between Fe metabolism and proliferation and points to a novel mode of anticancer activity.

**Tachpyridine.** N,N′,N′′-tris(2-pyridylmethyl)-cis,cis-1,3,5-triaminocyclohexane (tachpyridine or tachpyr; Fig. 2) is a hexadentate chelator (37). Tachpyridine is cytotoxic to bladder cancer cells with an IC$_{50}$ of 4.6 μmol/L compared with 70 μmol/L for deferoxamine (37). Although tachpyridine binds Ca(II), Mg(II), Mn(II), Cu(II), and Zn(II), toxicity studies with tachpyridine complexes suggest that Fe depletion mediates its cytotoxic effects (37).

Similar to Triapine and Dp44mT, tachpyridine induces apoptotic death independent of functional p53 (38, 39). Furthermore, tachpyridine-induced death was prevented in cells microinjected with Bcl-X$_L$ and a dominant-negative caspase-9 expression vector, suggesting activation of the mitochondrial apoptotic pathway (39). In addition, tachpyridine-Fe complexes produce *OH or hypervalent Fe through the Haber-Weiss reaction, which contributes to its antitumor activity (40).

Interestingly, tachpyridine arrests cells at G$_2$, which is a radiosensitive phase of the cell cycle (41). In fact, radiation increased the sensitivity of tumor cells to the action of tachpyridine (41). This result was unexpected because most Fe chelators arrest cells at the G$_1$-S interface due to inhi bition of ribonucleotide reductase (16). Tachpyridine binds Fe, but it can also bind Cu(II) and Zn(II), which may underlie its...
ability to arrest cells in G2 (37). Currently, tachpyridine is in preclinical development with the National Cancer Institute (41), and evaluation of tachpyridine derivatives, such as trenpyr, are under way (42).

**Copper and Cancer Therapy**

The dependence of tumor growth on angiogenesis was first hypothesized by Folkman (43). This theory suggested that angiogenesis inhibitors might be useful cancer chemotherapeutics. In fact, angiogenesis was found to be important for metastasis (44, 45). It has long been known that Cu plays an essential role in angiogenesis (6). Pioneering studies showed that Cu became concentrated in the rabbit cornea during neovascularization (46). More recently, Cu was found to be important in the expression or function of many angiogenic factors, including fibronectin; collagenase; gangliosides; prostaglandin E1; angiogenin; S100A13; fibroblast growth factor-1; secreted protein, acidic, cysteine-rich; synaptotagamin; vascular endothelial growth factor-1; IL-1, IL-6, and IL-8; and nuclear factor-κB (review ref. 6).

A recent study has linked Cu with the activation of hypoxia inducible factor-1α (47). This potentially holds great significance, as hypoxia inducible factor-1α regulates the expression of the proangiogenic molecules nitric oxide synthase and vascular endothelial growth factor-1 (48, 49). Another study suggested that ceruloplasmin, the proangiogenic serum Cu transport protein, is also partly regulated by hypoxia inducible factor-1α–dependent promoter activation (47).

Collectively, the requirement of Cu for angiogenesis suggests a role for Cu-chelating drugs in targeting tumor angiogenesis and metastasis, particularly in hypervascularized tumors (7, 50, 51).

**Penicillamine and trientine.** The copper chelators penicillamine and trientine (Fig. 3) are used in the treatment of the copper-loading disease, Wilson’s disease (52). The success of these chelators in treating copper toxicity has led to their examination as angiogenesis inhibitors against cancer.

A landmark study compared the invasiveness of the VX2 rabbit brain carcinoma in normocupremic animals relative to rabbits copper-depleted by diet and penicillamine (53). Normocupremic rabbits developed large vascularized VX2 carcinomas, whereas small and relatively avascular tumors were found in copper-depleted rabbits (53). However, in a phase II clinical trial, penicillamine, in combination with a low Cu diet, resulted in no improvement in survival of patients suffering glioblastoma multiforme (54). Hence, further, studies with penicillamine are necessary to judge whether it has any place in chemotherapy.

Studies with the Cu chelator, trientine, also showed suppressed tumor development and angiogenesis in vivo (55). In comparison with penicillamine, trientine was more effective at inhibiting growth of a murine hepatocellular carcinoma xenograft model and resulted in marked suppression of neovascularization (55). More recently, trientine, in combination with methotrexate, exerted a tumoricidal effect in a human colorectal carcinoma xenograft in mice and led to “tumor dormancy” (56). However, these promising results remain to be confirmed in clinical trials.

**Tetrathiomolybdate.** The Cu chelator tetrathiomolybdate is another example of a ligand originally developed for Wilson’s disease that inhibits angiogenesis and reduces tumor growth (7, 57). This promising antiangiogenesis agent induced Cu deficiency and suppressed tumor growth in the SUM 149 murine breast cancer xenograft model to 31% of untreated controls (7). Reduction in vascular density and tumor metastases had also been reported in tetrathiomolybdate-treated mice bearing SUM149 breast cancer xenografts (7).

The activity of tetrathiomolybdate has been attributed to its ability to form a high-affinity tripartite complex with copper and albumin, to chelate copper from the bloodstream, and to suppress the nuclear factor-κB signaling cascade (58). This reduces expression of angiogenic mediators, including vascular endothelial growth factor-1, fibroblast growth factor-1, IL-1a, IL-6, and IL-8 (58).

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**Fig. 3.** Chemical structures of the copper-binding chelators, trientine (tetrathylethylene tetramine), tetrathiomolybdate, and D-penicillamine.
Further studies with tetrathiomolybdate assessed its antiangiogenic activity in combination with other treatments. One study showed that tetrathiomolybdate and doxorubicin was more effective than either single agent in the murine SUM149 xenograft model (59). Most recently, tetrathiomolybdate was combined with radiation treatment and assessed against tumor growth in a mouse model of head and neck squamous cell carcinoma (60). Mice receiving tetrathiomolybdate plus radiotherapy showed a significant decrease in tumor growth compared with mice receiving either tetrathiomolybdate or radiotherapy alone (60).

The promising activity of tetrathiomolybdate has led to its investigation in clinical trials (Table 1; refs. 51, 61). In the most recently published trial, tetrathiomolybdate suppressed the proangiogenic factors: basic fibroblast growth factor 1, IL-6, IL-8, and vascular endothelial growth factor-1 in patients with advanced metastatic kidney cancer (51). As a single agent, stable disease was observed in 31% of patients, but it was concluded that this response was not significant (51). These authors further concluded that tetrathiomolybdate may need to be combined with other antiangiogenic therapies to be effective (51). Indeed, clinical trials with tetrathiomolybdate in combination with other agents are under way.

Conclusions

Observations that rapid neoplastic cell proliferation requires Fe have led to the demonstration that some Fe chelators may be useful against cancer. Currently, the Fe chelator Triapine is being examined in clinical trials, with focus on its potential in combination therapy. The search for more effective chelators has led to the development of other potent ligands, including Dp44mT and tachyphilin. However, further in vivo and preclinical studies will be necessary to build on their promise.

The discovery of the role of Cu in angiogenesis led to the postulation that Cu chelators maybe useful angiogenesis inhibitors. The most promising of these is tetrathiomolybdate, which has produced significant in vitro and in vivo results. However, trials with tetrathiomolybdate as a single agent have not been highly successful. Further studies may identify an effective combination with other agents or point to the need to develop more effective Cu chelators for antiangiogenesis therapy.

Irrespective of the fate of the chelators discussed in this review, it is apparent that “proof of principle” data exist to justify positioning these agents at the cancer treatment coalface.

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