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Targeting hematologic malignancies by inhibiting *E*-selectin: A sweet spot for AML therapy?

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Abstract

E-selectin, a cytoadhesive glycoprotein, is expressed on venular endothelial cells and mediates leukocyte localization to inflamed endothelium, the first step in inflammatory cell extravasation into tissue. Constitutive marrow endothelial E-selectin expression also supports bone marrow hematopoiesis via NF-κB-mediated signaling. Correspondingly, E-selectin interaction with E-selectin ligand (sialyl Lewis^x) on acute myeloid leukemia (AML) cells leads to chemotherapy resistance in vivo. Uproleselan (GMI-1271) is a carbohydrate analog of sialyl Lewis^x that blocks E-selectin binding. A Phase 2 trial of MEC chemotherapy combined with uproleselan for relapsed/refractory AML showed a median overall survival of 8.8 months and low (2%) rates of severe oral mucositis. Clinical trials seek to confirm activity in AML and mitigation of neutrophil-mediated adverse events (mucositis and diarrhea) after intensive chemotherapy. In this review we summarize

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Declaration of competing interest

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.blre.2024.101184.

E-selectin biology and the rationale for uproleselan in combination with other therapies for hematologic malignancies. We also describe uproleselan pharmacology and ongoing clinical trials.

Keywords

Uproleselan; E-selectin; Selectin; Acute myeloid leukemia (AML); Hematologic malignancies

1. Introduction

Successful treatment of acute myeloid leukemia (AML) began with cytosine arabinoside (Ara–C), approved by the FDA in 1969 [1] and later improved via combination with anthracyclines in the 1970s [2,3]. As a single agent, high dose Ara-C [4] is still used for consolidation of AML after induction. The Cancer and Leukemia Group B established superiority of 7-day continuous infusion of cytosine arabinoside with 3 days of intermittent daunorubicin infusions ("7 + 3") that remains the standard approach for induction of AML in adults [5]. Idarubicin, another anthracycline, was shown to be effective in combination with cytosine arabinoside in the 1990s [6,7], and a liposomal formulation of cytarabine and daunorubicin (VYXEOS) was approved in 2017 [8,9]. Additional improvements in AML treatment include small molecule inhibitors targeting IDH1 (ivosidenib) [10], IDH2 (enasidenib) [11], and FLT3 (midostaurin and quizartinib) [12,13] mutations, as well as BCL2 (venetoclax) [14], though these targeted therapies are usually given with standard chemotherapy combinations. Nonetheless, most of these mutations are found only in a minority of AML patients, and resistance usually develops to all these agents [15,16], so high unmet need persists for better AML treatments.

Endothelial (*E*)-selectin is an adhesion protein that promotes leukocyte tethering and rolling, thus controlling neutrophil and monocyte trafficking, and stimulates hematopoietic stem cell and progenitor cell proliferation in the bone marrow [17]. E-selectin also influences pro-survival signaling in hematologic cancers and potentially fosters chemotherapy resistance. Recently, inhibitors of E-selectin have been identified that might overcome chemotherapy resistance of AML [18]. One such E-selectin antagonist in advanced clinical trials, uproleselan (GlycoMimetics, Rockville, MD), shows promise as therapy for relapsed/refractory (R/R), as well as untreated AML.

This review focuses on E-selectin's role in normal hematopoiesis and hematologic malignancies, as well as E-selectin inhibition to treat hematologic diseases, especially AML. We describe structure and function of selectins, in particular E-selectin, pharmacology and biologic activity of E-selectin antagonist uproleselan in pre-clinical models and clinical trials in AML and multiple myeloma.

2. E-selectin structure, function, and biology

2.1. Selectins

Selectins are cell surface glycoproteins that mediate cell-to-cell adhesion of leukocytes to endothelial cells that line the vasculature. This protein family's name derives from their binding to cell surface carbohydrates on leukocytes [19]. Three homologous selectins are

further named to reflect their cells of origin, including E-selectin in endothelial cells, *P*-selectin in platelets, and *L*-selectin in lymphocytes. Selectins are "C-type lectins" that rely on simultaneous binding to carbohydrate ligands and to calcium (Ca^{++}) for biologic activity. E-selectin binds an oligosaccharide carbohydrate structure shared by both sialyl Le^a and sialyl Le^x [20,21].

Multiple synonyms have been used to describe each selectin protein, based on method of discovery. Supplemental Table 1 lists synonyms for each. In this review we refer to these various proteins as E-selectin, P-selectin, and L-selectin.

As described above, selectins mediate leukocyte rolling and tethering to endothelium that facilitates extravasation of leukocytes into tissue. E-selectin binds leukocytes to activated endothelium, whereas P-selectin binds leukocytes to platelet-activated endothelium and platelets, and L-selectin binds leukocytes to lymph node high endothelial venules (HEVs).

Collins et al. [22] established that the E-selectin gene comprises 14 exons coding for lectin, epidermal growth factor (EGF), short consensus repeat (SCR), transmembrane, and cytoplasmic domains. The three selectin genes reside in a ~ 150,000 bp stretch of DNA on chromosome 1 at 1q24, presumably evolved from duplication of a common ancestor gene [23] Fig. 1.

2.2. E-selectin biology

2.2.1. E-selectin role in acute inflammation—E-selectin expression is limited to endothelial cells, induced by NF-κB signaling after endothelial cell exposure to innate inflammatory mediators, including TNFα, IL-1β, and lipopolysaccharide [31]. Also, while P-selectin is stored in endothelial cell Weibel-Palade bodies and platelet storage granules, E-selectin is not stored in any intracellular compartment. Hence, endothelial E-selectin expression is driven by inflammatory cytokines, whereas P-selectin secretion occurs via exocytosis of endothelial stores after stimulation by activated platelets [24,32].

E-selectin is a carbohydrate binding protein that, after ligand binding, undergoes a conformational change that increases bond strength with increasing shear, until failure, known as a "catch bond". In contrast, conventional bonds do not increase in strength with increased shear forces. Molecular dynamics simulations of *E*-selectin co-crystalized with its carbohydrate binding ligand reveal a transition to a high affinity state [33]. Small angle X-ray scattering experiments [33] also support empirical data on catch bond properties demonstrated with cells tethering to ligands under shear forces in vitro [34].

Endothelial E-selectin leads to myeloid cell binding, rolling, and tethering on local endothelium. Another key functional property of E-selectin expressed at sites of inflammation is its ability when bound to induce leukocyte-expressed adhesion molecules called integrins to enter a high affinity state [33,34]. This change causes leukocyte arrest on endothelium and firm adhesion of cells in the bloodstream at this site. Contact with E-selectin can also mediate release of chemokines from myeloid cells, attracting other leukocytes [35]. In summary, endothelial E-selectin expression induced by cytokines at sites of inflammation leads to neutrophil binding, rolling, and tethering on local endothelium.

Cell-cell binding occurs between neutrophil surface sialyl Lewis^x tetrasaccharides and endothelial surface E-selectin, forming catch-bonds that lead to neutrophil arrest, then extravasation into tissue, as shown in Fig. 2.

2.2.2. Animal models of E-selectin deficiency: Role in neutrophil recruitment and lymphocyte function—Animal models illuminate selectin protein roles in neutrophil and lymphocyte function. E-selectin knockout (*Sele*$^{-/-}$) mice have normal blood indices with no obvious disease phenotype [36,37]. Conversely, double knockout (*Sele*$^{-/-}$ *Selp*$^{-/-}$) mice deficient in both E- and P-selectin display high neutrophil counts, lymphadenopathy, ulcerative dermatitis, conjunctivitis, and lung pathology, contributing to a shortened lifespan [38,39]. Curiously, triple knockout (*Sele*$^{-/-}$ *Selp*$^{-/-}$ *Sell*$^{-/-}$) mice lacking E-, P-, and L-selectins have only elevated leukocyte counts with none of the other lymphocyte-mediated immune pathologies of double knockout mice [39]. Similarly, triple knockout mice (*Sele*$^{-/-}$ *Selp*$^{-/-}$ *Rag-1*$^{-/-}$) lacking E- and P-selectin and without any mature T or B lymphocytes do not develop ulcerative dermatitis, as seen in E- and P-selectin double knockout mice [38]. The ability to extrapolate these findings to human disease is tempered by the caveat that in mice E- and P-selectin expression are both induced by inflammatory mediators, such as TNFα and IL1β. By contrast, in humans and other primates only E-selectin expression is so induced; P-selectin is not [40–42].

2.2.3. Role of E-selectin in hematopoietic stem cell homeostasis—Hematopoietic stem cells (HSCs) generate progenitor cells upstream of erythrocyte, leukocyte, and platelet production. The most potent HSCs, with heightened regenerative potential upon transplantation, are located in bone marrow and enriched in the endosteal/osteoblastic microenvironment within a few cell diameters from bone interface [43], and/or adjacent to blood vessels [44]. Compared with other tissues bone marrow is a relatively "inflamed" environment where E-selectin is constitutively expressed by a portion of marrow endothelial cells. In this location E-selectin has been demonstrated to be one of the signals driving the commitment of potent HSCs towards production of blood and immune cells at the expense of HSC regeneration [17]. In addition, E-selectin, together with P-selectin also facilitates homing of transplanted CD34$^+$ hematopoietic stem and progenitor cells to bone marrow [45,46]. In mice where E-selectin is absent (*Sele*$^{-/-}$) or blocked, a greater proportion of HSCs remain quiescent with heightened regenerative potential following serial transplants in wild type mice [17].

2.2.4. E-selectin and human disease—E-selectin knockout (*Sele*$^{-/-}$) mice have no obvious disease phenotype [36,37], and there appear to be no human diseases associated with E-selectin deficiency. In contrast, presence of a common polymorphism in the E-selectin EGF domain (S128R) in which serine is more prevalent and arginine is less prevalent associates with premature atherosclerosis [47,48]. Soluble E-selectin levels in blood are higher with type O (and lower with type A1) ABO blood group alleles [49] and associate with severity of pulmonary hypertension and organ dysfunction in sickle cell disease [50]. Rivipansel (GMI-1070) is a pan-selectin inhibitor that primarily inhibits E-selectin (IC50 = 4.3 μM) with lesser activity against P-selectin (IC50 = 423 μM) and L-selectin (IC50 = 337 μM) [51]. A clinical trial of E-selectin antagonist rivipansel to treat

hospitalized sickle cell patients with acute vaso-occlusive crisis failed to show rivipansel treatment benefit in the overall group. Yet post-hoc analysis showed evidence of benefit for patients treated within 26.4 h of symptoms (the earliest treatment quartile) for the primary endpoint (time to readiness for discharge), as well as two key secondary endpoints (time to discharge and time to discontinuation of intravenous opioids) [52].

2.2.5. E-selectin ligand—E-selectin binds target cells to endothelium via a surface ligand that is common to two carbohydrate structures initially discovered as tumor markers [20,53,54]. Sialyl Le^a, also known as cancer marker CA19–9 [55,56], and sialyl Le^x [57], also known as CD15s, are detected on leukocyte surfaces and are elevated on tumor cell surfaces [58,59].

Tetrasaccharide components of sialyl $Lewis^{a/x}$ are produced by sequential action of several glycosyltransferase enzymes. Terminal sugars (sialic acid and fucose) are added to the growing carbohydrate chain in order: first sialic acid by sialyltransferases, then fucose by fucosyltransferases. Humans express various sialyltransferases (ST3Gal3, ST3Gal4 and ST3Gal6) [60] and fucosyltransferases (FT3, FT4, FT5, FT6, FT7, and FT9) [61] that synthesize selectin ligands. Different enzymes are expressed, depending on cell type, but in all cases sialic acid addition precedes fucosylation. In human myeloid cells, ST3GAL4 encodes a principal catalyst of sialyl $Lewis^x$ synthesis, as shown by RNA silencing and Cas9 knockdown/knockout experiments [62]. Fucosyl transferase 7 (FUT7) catalyzes the final fucosylation in sialyl $Lewis^x$ synthesis [63].

The GDP-fucose transporter is necessary for synthesis of sialyl $Lewis^x$, the neutrophil receptor for E-selectin. Its genetic deficiency leads to leukocyte adhesion deficiency type 2 disease (LADII), a rare disease found in Israeli Arabs that features leukocytosis, cellulitis, and inability to fight bacterial infection due to impaired neutrophil extravasation into tissues [64].

The trisaccharide domain common to sialyl Le^a and sialyl Le^x that forms the selectin binding epitope [20] is displayed on cell surface glycoproteins and glycolipids. An antibody, HECA-452, that binds this same carbohydrate epitope [20] has historically been used to identify functional selectin ligands on specific glycoproteins of various cell types. Cell surface glycoproteins displaying this carbohydrate epitope, such as PSGL-1 (CD162), CD44 and CD43, as well as L-selectin (CD-62 L) act as functional ligands for selectins across cell types. Glycoforms of PSGL-1 (CD162), CD44, and CD43 that display selectin ligands by HECA-452 antibody detection are known as cutaneous lymphocyte antigen (CLA) [65], Hematopoietic Cell E/L-selectin Ligand (HCELL) [66], and CD43E (CD43 decorated with CLA epitope) [67], respectively.

3. Hematologic malignancies as targets for *E*-selectin inhibition

3.1. E-selectin ligand expression in hematologic malignancies

Interaction of malignant cells with E-selectin facilitates transendothelial migration and metastasis. Moreover, adhesion within the tumor or marrow microenvironment confers drug resistance. Several studies of human cancer, as well as in preclinical animal models,

show that E-selectin antagonism appears both to improve chemotherapy effectiveness in hematologic malignancies and to mitigate adverse therapy side-effects, such as mucositis and diarrhea.

Table 1 lists lines of evidence for therapeutic inhibition of E-selectin as a therapeutic strategy for treatment of hematologic malignancies and mitigation of adverse events (mucositis).

3.2. E-selectin ligand expression in AML

E-selectin ligand-mediated adhesion affects proliferation and bone marrow niche localization of leukemia-regenerating cells that produce leukemic AML blasts [68]. This effect is analogous to E-selectin's role in controlling niche localization of normal hematopoietic stem cells. However, outcomes of E-selectin adhesion differ in HSC versus AML cells. For HSC E-selectin adhesion promotes differentiation and lineage commitment [17], while in AML blasts E-selectin adhesion promotes survival and chemotherapy resistance, in particular among the small subpopulation of AML blasts able to regenerate disease, often referred to as leukemia stem cells. This E-selectin mediated chemotherapy resistance depends on cell surface presence of sialyl Lewis^x glycosylation [18].

In a series of 89 AML patients, expression of E-selectin ligand by leukemic stem cells of individual patients correlated with expression by their AML blasts (correlation coefficient 0.90, $P < 2.2 \times 10^{-16}$) [69]. Conversely the percent of leukemic blasts expressing functional E-selectin ligand was greater in relapsed than in untreated patients (38% vs. 25%, respectively, $P = 0.037$) and similarly greater in patients with unfavorable than favorable/intermediate risk cytogenetics (39% vs. 24%, respectively, $P = 0.033$). E-selectin ligand measured on blasts was lower in FLT3-ITD mutated than non-FLT3-ITD mutated AML ($P = 0.042$) and similarly lower in NPM1 mutated than non-mutated AML ($P = 0.038$) [69].

AML blasts may secrete inflammatory cytokines that further upregulate E-selectin expression [18] and contribute to increased circulating levels of E-selectin (surface cleaved "soluble E-selectin" or sE-selectin) levels observed in patients with untreated AML [70]. Baseline sE-selectin levels were increased in sera of patients with newly diagnosed AML, compared with that in serum of healthy subjects [70–72]. Two studies showed that increased sE-selectin levels correlated with extramedullary infiltration of AML cells ($P < 0.001$) and predicted relapse ($P < 0.01$); sE-selectin levels at AML diagnosis predicted low survival ($P < 0.001$); and decreased sE-selectin levels after treatment correlated with durable AML remission [71,73]. AML blasts bound to E-selectin are resistant to chemotherapy effects in vitro, and this cell-adhesion mediated drug resistance, or CAMDR, in mouse experiments has been demonstrated to be a source of relapse in vivo [18,74]. In patients, E-selectin inhibition is hypothesized to disrupt AML blast adhesion in the bone marrow niche, thus dampening E-selectin mediated AML cell survival signaling. Together these findings support a relationship between marrow E-selectin and AML prognosis and suggest that leukemic blasts expressing E-selectin ligand may contribute to R/R disease.

3.3. E-selectin inhibition as a therapeutic strategy for treatment of AML

Expression of E-selectin or its binding epitope (sialyl Lewis$^{a/x}$) may predict clinical course and patient outcomes in AML [70–73,75]. Leukemic blasts expressing the E-selectin ligand adhere to E-selectin expressed on bone marrow microvasculature, mediating chemoresistance that can be reversed by E-selectin inhibition [76,77]. Inhibition of E-selectin may overcome chemotherapy resistance by altering the bone marrow microenvironment contribution to leukemogenesis [78] and/or by displacing leukemic cells from that protective niche.

3.4. Uproleselan, a selective inhibitor of E-selectin

Both sialyl Le^{a} and sialyl Le^{x} bind E-selectin [20]. By comparing 3-dimensional structures of these 2 different carbohydrates a common trisaccharide domain was discovered that identifies the precise epitope for binding E-selectin. Monoclonal antibody HECA-452 that binds to both sialyl Lewis^{a} and sialyl Lewis^{x} [20] has been used to detect E-selectin ligand on cell surfaces.

Knowledge of E-selectin binding epitope structure enabled molecular design of glycomimetic compounds with therapeutic properties. Glycomimetic uproleselan (GMI-1271) potently inhibits interaction between E-selectin and its receptor, sialyl Lewis^{x} [79]. Uproleselan mimics structure of E-selectin ligand sialyl Lewis$^{a/x}$ and retains critical interactions with the E-selectin lectin domain, also known structurally as the carbohydrate recognition domain (CRD). Uproleselan has a 12-mer polyethylene glycol (PEG) tail to enhance its pharmacologic properties (Fig. 3).

Uproleselan's interaction with E-selectin was modeled in silico by docking into the crystal structure of the E-selectin CRD. The trisaccharide of fucose stacked under galactose with a terminal sialic acid makes intimate contact with the E-selectin CRD, as shown in Fig. 4.

3.5. Animal models of Uproleselan activity in AML

Anti-leukemia activity of uproleselan in combination with cytosine arabinoside/daunorubicin (AraC/DNR), cytosine arabinoside/doxorubicin (AraC/DOX), 5-azacytidine (AZA), or venetoclax/5-azacytidine (VEN/AZA) was assessed in five distinct experimental models of AML, including 4 in NOD-SCID mice, shown in Fig. 5. In experiments with fresh human AML cells infused into mice, addition of uproleselan, 10 mg/kg IP BID or 40 mg/kg IP BID for 10 days, to AraC/DNR chemotherapy improved median survival of leukemic mice ($P = 0.0031$, and 0.0143, respectively) compared to chemotherapy alone (Fig. 5A) [82]. Similar experiments with U937 human AML cells showed that addition of uproleselan 40 mg/kg IP BID for 9 days to AraC-DNR chemotherapy improved median survival time, compared to chemotherapy alone ($P = 0.0562$) (Fig. 5B) [82].

In NOD-SCID mice infused with the KG1-luc human AML cell line (Fig. 5C), addition of uproleselan 40 mg/kg IP QD for 14 days to AZA chemotherapy significantly improved median survival of leukemic mice over chemotherapy alone ($P = 0.014$) [83].

When uproleselan 40 mg/kg IP QD was added to VEN/AZA treatment of NOD-SCID mice infused with leukemic cells from a patient with FLT3-ITD, NRAS, and GATA2

mutations and resistance to VEN/AZA chemotherapy (Fig. 5D) resistance to chemotherapy was reversed, indicated by significant improvement in median survival ($P < 0.001$) compared to chemotherapy alone [84].

Finally, addition of uproleselan 40 mg/kg IP BID for 10 days to AraC/DOX chemotherapy significantly ($P = 0.0054$) prolonged median survival of C57BL/6 mice infused with monomyelocytic leukemia cells induced by retroviral *MLL-AF9*-ires-GFP, compared to AraC/DOX chemotherapy alone (Fig. 5E) [18].

In every model tested there was synergy between uproleselan and chemotherapy when combined to treat experimental leukemia. Importantly, in no experimental model was there evidence for single agent activity of uproleselan alone at the dose levels tested suggesting that uproleselan mainly renders leukemic cells sensitive to effects of chemotherapeutic agents. These data are consistent with expectations based on mouse gene knockout results and provide justification for clinical trials of uproleselan in combination with chemotherapy (or epigenetic modifiers) for AML.

3.6. Animal models of Uproleselan activity in multiple myeloma

Uproleselan improves activity of proteasome inhibitors bortezomib or carfilzomib in mouse models of multiple myeloma. Addition of uproleselan to bortezomib treatment of NOD-SCID mice infused with a high E-selectin ligand-expressing subclone of MM1S myeloma cells increased survival significantly ($P = 0.0025$), compared to bortezomib alone [85]. Similar results were seen with the 5TGM1 multiple myeloma cell line engrafted in C57BL/ KaLwRijHsd mice, where addition of uproleselan to carfilzomib treatment improved survival significantly ($P < 0.05$) [86]. In SCID mice engrafted with human MM1S myeloma cells, more aggressive, bortezomib-resistant disease resulted after enrichment for higher levels of E-selectin ligand expression ($P = 0.0005$) [87]. Still, addition of GMI-1271 (uproleselan) to bortezomib increased survival of mice engrafted with either parental MM1S cells ($P = 0.0363$) or MM1S cells selected for high E-selectin ligand expression ($P = 0.0123$). [87].

3.7. E-selectin and chemotherapy-induced diarrhea and Oral mucositis

Diarrhea and mucositis are common side effects of cytotoxic chemotherapy for hematologic malignancies. Mucositis can be a debilitating effect of combination chemotherapy regimens that include anthracyclines, etoposide, or melphalan. Severe mucositis, especially with concurrent cytopenias, increases risks of infection, hospitalization, poor quality of life, and death [88]. Importantly, secondary leukocyte infiltration and activation has been shown to contribute to development of mucositis after cytotoxic chemotherapy [89].

E-selectin inhibition or genetic knockouts of the E-selectin gene are reported to protect against chemotherapy side effects of neutropenia and mucositis [90]. E-selectin antagonists, when given as an adjunct therapy to 5-fluorouracil, enhanced neutrophil recovery [17] and reduced weight loss and mucositis severity after chemotherapy, compared with mice treated with 5-fluorouracil alone [90].

E-selectin deficiency or inhibition has been shown in animal models to protect against these side effects. Also, uproleselan has been shown in clinical trial GMI-1271-201 to improve mucositis rates after mitoxantrone, etoposide, cytarabine (MEC) chemotherapy of AML [91], discussed in Section 5.1.

4. Pharmacology and toxicology of Uproleselan

4.1. Preclinical pharmacology of Uproleselan

Uproleselan is a small molecule that is eliminated by renal excretion with little pre-clinical evidence of hepatic metabolism, drug-drug interactions, or mutagenicity. In vitro and in vivo preclinical studies are described in detail in the Preclinical Pharmacology Supplement to this paper.

4.2. Human pharmacokinetics

Uproleselan pharmacokinetics (PK) have been evaluated in four clinical trials listed in Table 2.

Clinical trials GMI-1271–101, − 102, and − 104 assessed uproleselan PK in healthy subjects. These studies showed that at clinically relevant doses (≥ 10 mg/kg daily for 1 to 8 days) approximately 75% of administered doses were eliminated unchanged into urine. Over a broad range of doses (2–20 mg/kg), clearance did not vary with dose or over time (comparing Day 1 to Day 5) [92,97]. PK parameters at the proposed Phase 2/3 dose across studies are compared in Supplemental Table 2. There was good agreement in reported PK parameters across studies and between healthy subjects and patients with AML. GMI-1271-201 was a Phase 1/2 multicenter, open-label trial of uproleselan combined with chemotherapy in adults with AML [91]. Uproleselan t½ was short at 1.51 to 2.47 h in healthy subjects using non-compartmental analysis [92,96,98], indicating that after multiple dosing (every 12 h or once daily) each dose would behave like a single dose with minimal accumulation. In the GMI-1271-201 study, a t½ of 3.43 h using compartmental analysis with population methods is comparable to that seen in healthy subjects. Cmax, CL, and Vz values likewise are comparable between healthy volunteers and AML patients.

In clinical trial GMI-1271–104, healthy men received a single IV dose of ^{14}C-labeled uproleselan to assess mass balance, and there was complete recovery of radioactivity [96]. Complete urinary excretion (~100%) and < 2% dose recovery in feces confirm that renal excretion is the primary route of elimination. Also, < 2% of a single metabolite (GMI-1271-desfucose) was recovered in urine, indicating minimal metabolism [96].

Of 91 subjects in clinical trial GMI-1271-201, 59 were included in PK analyses. Phase 1 and Phase 2 Arm A included subjects ≥18 years with R/R AML eligible to receive MEC induction chemotherapy. Phase 2 Arm B included subjects ≥60 years of age with newly diagnosed AML eligible to receive cytarabine/idarubicin (7 + 3) induction chemotherapy. For all patients, uproleselan was first given 1 day before start of induction chemotherapy, then every 12 h on chemotherapy days and for 2 days after chemotherapy.

A population pharmacokinetic (PPK) model was fitted using mixed-effects methods with NONMEM software [97,99,100]. Uproleselan clearance varied with renal function, consistent with the large fraction of unchanged drug eliminated renally. Also, clearance was 13% lower in women, compared to men, a difference not considered to be clinically meaningful.

The impact of renal function on uproleselan clearance in GMI-1271-201 trial patients is shown in Supplemental Figs. 1 and 2, and PK parameters are summarized in Supplemental Table 2.

4.3. Human pharmacodynamics: Efficacy

Relationships were assessed among clinical outcomes, efficacy biomarkers, time, and exposure in the GMI-1271-201 clinical trial. C_{max} and AUC exposure metrics were obtained using post hoc (individual) parameter estimates from the optimal pharmacokinetic model described above. There was no apparent relationship between uproleselan exposure and survival. Median overall survival was longer ($P = 0.014$) for subjects with >10% of their AML blasts expressing E-selectin ligand (10.7 months), compared to those in whom <10% of AML blasts expressed E-selectin ligand (5.2 months) [91]. Conversely, in newly diagnosed patients there was no apparent relationship between E-selectin ligand levels and survival.

4.4. Human pharmacodynamics: Safety

In study GMI-1271-201, no relationships were observed between systemic uproleselan PK (AUC or Cmax) and anemia, neutropenia, thrombocytopenia, pancytopenia, febrile neutropenia, infection, mucositis, sepsis, hypoxia, pneumonia, or renal adverse events. Consistent with pre-clinical testing, clinical trials to date indicate no apparent safety concerns when uproleselan is combined with chemotherapy for AML or with conditioning for autologous stem cell transplant in multiple myeloma.

5. Clinical trials of Uproleselan

Acute myeloid leukemia (AML) was chosen for initial uproleselan development due to high unmet need from chemotherapy resistance, especially in R/R AML, known high level E-selectin ligand expression on AML blasts, and animal model activity described in Section 3.5. Uproleselan is being studied in adults with R/R or untreated AML, including untreated AML in patients over 60 years of age who are fit for standard induction chemotherapy, adults not fit for standard induction chemotherapy, and adults with treatment secondary AML.

In addition to overall survival and event-free survival, these studies evaluate as a secondary endpoint oral mucositis, a common adverse event with anthracyclines and etoposide chemotherapy. One investigator-initiated trial evaluates uproleselan effects on chemotherapy-induced diarrhea/mucositis in patients undergoing hematopoietic cell transplantation (HCT) for hematologic malignancies. Also, a Children's Oncology Group trial of uproleselan for pediatric patients with R/R AML is also underway. Ongoing

clinical trials of uproleselan for treatment of hematologic malignancies or amelioration of transplantation adverse events are listed in Table 3.

5.1. Hematologic malignancies

5.1.1. Relapsed/Refractory AML

5.1.1.1. Phase 1/2 trial of Uproleselan in adults with R/R or untreated AML.: A Phase 1/2 trial (GMI-1271-201, NCT02306291 at www.clinicaltrials.gov) evaluated safety, tolerability, and antileukemic activity of uproleselan (5–20 mg/kg IV twice daily for 8 days) with MEC chemotherapy in patients with R/R AML. No dose-limiting toxicities were observed in the first 19 patients treated in the Phase 1 portion of the trial, establishing 10 mg/kg IV twice daily for 8 days as the recommended Phase 2 dose [91]. An additional 47 patients with R/R AML were treated with MEC chemotherapy plus uproleselan 10 mg/kg twice daily for 8 days. Among 66 total patients treated at this dose, remission rate, including complete remission (CR) or CR with incomplete count recovery (CRi), was 41%; CR rate was 35%; and median overall survival (OS) was 8.8 months. Another key finding of this trial was that addition of uproleselan to MEC chemotherapy was associated with much lower rates of oral mucositis (2%) than seen in previous trials of MEC chemotherapy for R/R AML (19–25%) [91,101].

E-selectin ligand expression on leukemic blasts was higher in patients with relapsed vs primary refractory AML and in newly diagnosed older patients with high-risk cytogenetics and secondary AML. In the R/R cohort, E-selectin expression >10% was associated with a higher response rate and improved survival. High remission rates, low induction mortality, and low mucositis rates provided strong rationale for a Phase 3 randomized controlled trial of uproleselan in R/R AML.

5.1.1.2. A phase 3 clinical trial of Uproleselan or placebo with MEC or FAI combination chemotherapy for R/R AML (GMI-1271-301).: A pivotal trial enrolled 388 patients between November 2018 and November 2021 in nine countries across North America, Europe, the UK, and Australia to test benefit of uproleselan addition to MEC or FAI chemotherapy for R/R AML (GMI-1271-301, NCT03616470 at www.clinicaltrials.gov). Key eligibility criteria include age 18 to 75 years, primary refractory AML or AML in first or second relapse, with no more than one prior hematopoietic cell transplant. Investigators could choose MEC FAI chemotherapy for one cycle of induction and up to three cycles of consolidation with high- or intermediate-dose cytarabine (HiDAC/IDAC); patients were randomized to uproleselan or placebo after informed consent. Randomization to uproleselan or placebo was stratified by age < or ≥ 60, disease status, and induction chemotherapy. The primary endpoint is overall survival, with key secondary endpoints of rate of severe oral mucositis during induction, CR rate, and remission rate (CR/complete remission with incomplete hematologic recovery (CRh)).

Patients had median age of 58 years (range 20–75 years). Typical of R/R AML, 33.5% had refractory disease, and 66.5% had relapsed. Of relapsed patients, 19% and 81% had early (< 6 months) versus late relapse (≥ 6 months), respectively. ELN 2017 risk categorization [102] at trial entry was 42% adverse risk, 23% intermediate risk, 21% favorable risk, 14%

unknown. The Phase 3 study enrolled a marginally better ELN 2017 risk group than the Phase 1/2 trial [91].

In February of 2023 the independent Data Monitoring Committee (DMC) conducted an unblinded interim analysis of safety and recommended continuation until the originally planned final overall survival events trigger. The DMC expressed no concerns about safety. Final analysis is anticipated in the first half of 2024 and will reflect median follow-up of >3 years with at least 2 years of post-transplant data for the majority of surviving patients that received hematopoietic cell transplantation.

5.1.1.3. Phase 1b/2 clinical trial of Uproleselan with Cladribine and low-dose Cytarabine for treated secondary AML.: Treated secondary AML (ts-AML) is defined by prior chemotherapy treatment of an antecedent hematologic disorder. Prognosis is notably poor with median overall survival of under 5 months [103]. MD Anderson investigators initiated a Phase 1b/2 clinical trial (NCT04848974, available at www.clinicaltrials.gov) to assess safety, tolerability and efficacy of uproleselan (800 mg IV twice-daily for 12 days) combined with cladribine (3.75 or 5 mg/m^2 IV daily for 5 days) and low-dose cytarabine (LDAC; 15 mg or 20 mg SQ twice daily for 10 days). If required, reinduction was also with twice daily uproleselan. Consolidation was to be given if patients achieved CR, CRi, or morphologic leukemia-free state in bone marrow. In consolidation, cladribine was given for 3 days, and uproleselan was given once daily.

A preliminary report [104] has been published on the first 20 patients with a median age of 72 years and median follow up of 8.1 months. Prior diagnoses included 25% chronic myelomonocytic leukemia, 70% myelodysplastic syndrome (MDS), and 5% MDS/myeloproliferative neoplasm. All had unfavorable genetics by ELN 2022 criteria, and all had received prior methylating agents [104]. Also, 55% had received prior venetoclax, and 25% had prior hematopoietic cell transplantation. The most common adverse event was neutropenic fever in 65%, of which 2 cases were fatal. No dose-limiting toxicities occurred, and the higher chemotherapy dose levels were studied further. Eighteen patients were evaluable for response, including 11% CRi, 6% CRh, and 22% morphologic-leukemia free state. Blast reduction was seen in 72% of patients overall. Median cycles received was 1.5 (range 1–4), and median cycles at best response was 1 (range 1–2). Three patients received HCT following disease response. Median OS in these preliminary results was 5.3 months and the trial is ongoing.

5.2. Frontline treatment of AML

5.2.1. NCI-Alliance frontline therapy for elderly fit patients with AML—The Alliance for Clinical Trials in Oncology is conducting clinical trial A041701, a randomized Phase 2/3 trial of conventional intensive chemotherapy +/− uproleselan in older adults with AML (NCT03701308, available at www.clinicaltrials.gov). The trial enrolled subjects aged ≥60 years with untreated AML. Subjects were randomized to 7 + 3 induction with cytarabine 100 mg/m^2/day on days 1–7 by continuous IV infusion + daunorubicin 60 mg/m^2/day on Days 1–3, +/− uproleselan 800 mg IV on Day 1 and twice daily for Days 2–8. Subjects with residual disease on a Day 14 bone marrow biopsy received a second cycle

of induction (5 days cytarabine +2 days daunorubicin), +/− uproleselan. Those achieving a CR/CRi could receive up to 3 cycles of consolidation with intermediate dose cytarabine (2 g/m^2 continuous IV infusion, days 1–5), +/− uproleselan.

The primary Phase 2 objective is to evaluate event-free survival (EFS). A sample size of 262 patients was selected for the Phase 2 to detect an improvement in median EFS from 7 months to 11 months (HR = 0.64) with >95% power, using a log rank test. As of January 2024, the number of events required for Phase 2 readout was not reached.

5.2.2. AZA/VEN frontline AML (unfit or elderly)—Azacitidine plus venetoclax (AZA/VEN) is now standard of care for older or unfit patients with treatment-naïve AML based on Phase 1 [105] and Phase 3 data [14]. Yet only 23.4% of recipients achieve MRD negativity, including 41% of CR/CRi responders [106]. An ongoing Phase 1, open-label trial combines uproleselan with frontline AZA/VEN in AML patients at least 75 years of age or unfit for intensive chemotherapy (NCT04964505, available at www.clinicaltrials.gov). This trial confirmed safety of uproleselan 800 mg IV q12h for 7 days with AZA/ VEN, then proceeded to dose expansion [107]. Patients receive uproleselan with AZA 75 mg/m^2 IV/SC q24h for 7 days and VEN 400 mg PO daily for 28 days in 28-day cycles. Treatment continued until disease progression, intolerance, or patient decision to stop. A marrow biopsy is done after each cycle until achievement of a morphologic leukemia-free state or better response. Uproleselan is given for up to 6 cycles with dosing decreased from q12 hr to daily after reaching a morphologic leukemia-free state or better response. Primary objectives are safety and tolerability, and the secondary objective is to determine preliminary efficacy by assessment of MRD-negative CR/CRi rates.

Preliminary results were reported [107]. Eight patients [75% female, median age 78 (range 70–81)] were enrolled in dose optimization (n = 6) and dose expansion (n = 2). The most common grade 3 or higher treatment-emergent adverse events (TEAE) included anemia, thrombocytopenia, neutropenia, and febrile neutropenia. Fifty percent of patients experienced serious adverse events, with thrombocytopenia being the most common. The CR/CRi rate was 75% with response in cycle 1 occurring in 83% of CR/CRi responders. MRD negativity was 50% overall and 67% among CR/CRi responders. The study continues to enroll to further evaluate safety and efficacy of this regimen.

5.3. Mitigation of hematopoietic cell transplantation adverse events with Uproleselan

5.3.1. Mitigation of diarrhea in multiple myeloma patients undergoing Melphalan conditioning for hematopoietic cell transplantation—High dose melphalan preceding autologous hematopoietic cell transplantation (AHCT) for multiple myeloma is associated with gastrointestinal (GI) toxicity in >90% of patients [108] and remains a persistent high unmet need, despite supportive care such as ice chips or *N*-acetylcysteine [109–112]. Washington University investigators evaluated uproleselan for mitigation of chemotherapy-induced GI epithelial damage in a Phase 2, single-center, randomized, placebo-controlled trial (NCT04682405, available at www.clinicaltrials.gov). This study compared uproleselan versus placebo in 50 adults with myeloma receiving melphalan 200 mg/m^2 followed by AHCT. Patients received uproleselan 800 mg IV or

placebo every 12 h beginning on day −3 of the transplant. High dose melphalan was administered on day −2. Uproleselan or placebo continued every 12 h for a total of 6 doses with the final uproleselan dose given 4 h before transplant infusion. The primary endpoint was diarrhea severity (CTCAE v5.0) during days 1 to 14 after AHCT, and a one-sided significance level of $P < 0.2$ was pre-specified for all endpoints [113].

Diarrhea severity score (1.07 vs 1.19, 95% CI −0.28; 0.04, $P = 0.34$) was lower on uproleselan but did not meet statistical significance [113]. Nonetheless, incidence of Grade 3 diarrhea showed a trend towards improvement (odds ratio [OR] 0.61, 95% CI 0.35; 1.07, $P = 0.26$). Also, oral mucositis, GI patient-reported outcomes (NCI PRO-CTCAE v1.0), and health related quality of life all revealed evidence of clinical activity. Reduction in severe diarrhea (by the Bristol Stool Scale) favored uproleselan ($P = 0.10$) vs placebo, with an improvement in the uproleselan arm to mild diarrhea ($P = 0.02$). By Day 8 after AHCT patients in the uproleselan arm experienced significant improvement in severity of GI-related symptoms across 30% (6/20) of domains surveyed vs placebo ($P = 0.07–0.14$) [113]. Improved mouth sore-related symptoms continued to Day +14 after auto-HCT on uproleselan vs placebo ($P = 0.17$) [113]. There was no evidence of delayed hematopoietic recovery or time to neutrophil engraftment [114].

6. Future considerations

Findings from uproleselan clinical trials in AML provide rationale for additional trials in related conditions, such as myelodysplastic syndrome, particularly in patients with high-risk features. Also, given its novel mechanism and notably unremarkable safety profile, uproleselan might generate benefit in combination with other AML drugs, drug combinations, and/or therapeutic approaches, e.g. immunotherapies.

Another E-selectin inhibitor, GMI-1359, inhibits CXCR4 in addition to E-selectin. Both CXCR4 and E-selectin ligand are upregulated in FLT3-ITD mutated AML patient blasts, and GMI-1359 with quizartinib treatment improved survival of immunodeficient NSG mice implanted with FLT3-ITD mutated AML [115]. These pre-clinical experiments provide rationale for additional testing of GMI-1359 in treatment of FLT3-ITD mutated AML.

Ongoing trial results of uproleselan with HCT conditioning for chemotherapy resistant AML (Table 3) may extend our understanding of uproleselan effects on chemotherapy resistance and mucositis. Further, trials of uproleselan with immunomodulators or chemotherapy for multiple myeloma could confirm findings in animal models of multiple myeloma (Section 3.6).

Relationships among E-selectin ligand expression on AML blasts, uproleselan-mediated survival improvement, and severe oral mucositis rates comprise key research questions to address. For example, uproleselan clinical activity in AML might depend on E-selectin ligand expression on AML blasts, whereas any benefits severe oral mucositis rates presumably will not. Accordingly, patients with AML and high levels of E-selectin ligand on their blasts may realize a direct benefit from combination of uproleselan with chemotherapy, while patients with low levels of E-selectin on their AML blasts might still realize indirect

benefits from less severe oral mucositis from chemotherapy. These important questions will be answered in clinical trials underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Practice points

Caveat: uproleselan remains an Investigational Drug, not FDA-approved for any indication. If the pivotal clinical trial confirms findings of the open label GMI-1271-201 clinical trial, then:

- Uproleselan may synergize with salvage chemotherapy (e.g., MEC, FAI) to overcome chemotherapy resistance in R/R AML
- Uproleselan may synergize with chemotherapy to improve survival in frontline AML treatment with standard regimens, such as 7 + 3.
- Uproleselan may reduce severe and other adverse events associated with AML chemotherapy and HCT conditioning

Research Agenda

- Ongoing efforts to ascertain clinical utility of adjunctive uproleselan therapy across AML and other hematologic malignancies
- Further research to illuminate the role of E-selectin ligand in uproleselan clinical activity
- Further research to illuminate utility of soluble E-selectin to predict uproleselan efficacy
- Mechanism(s) of AML chemotherapy resistance due to AML blast binding to E-selectin

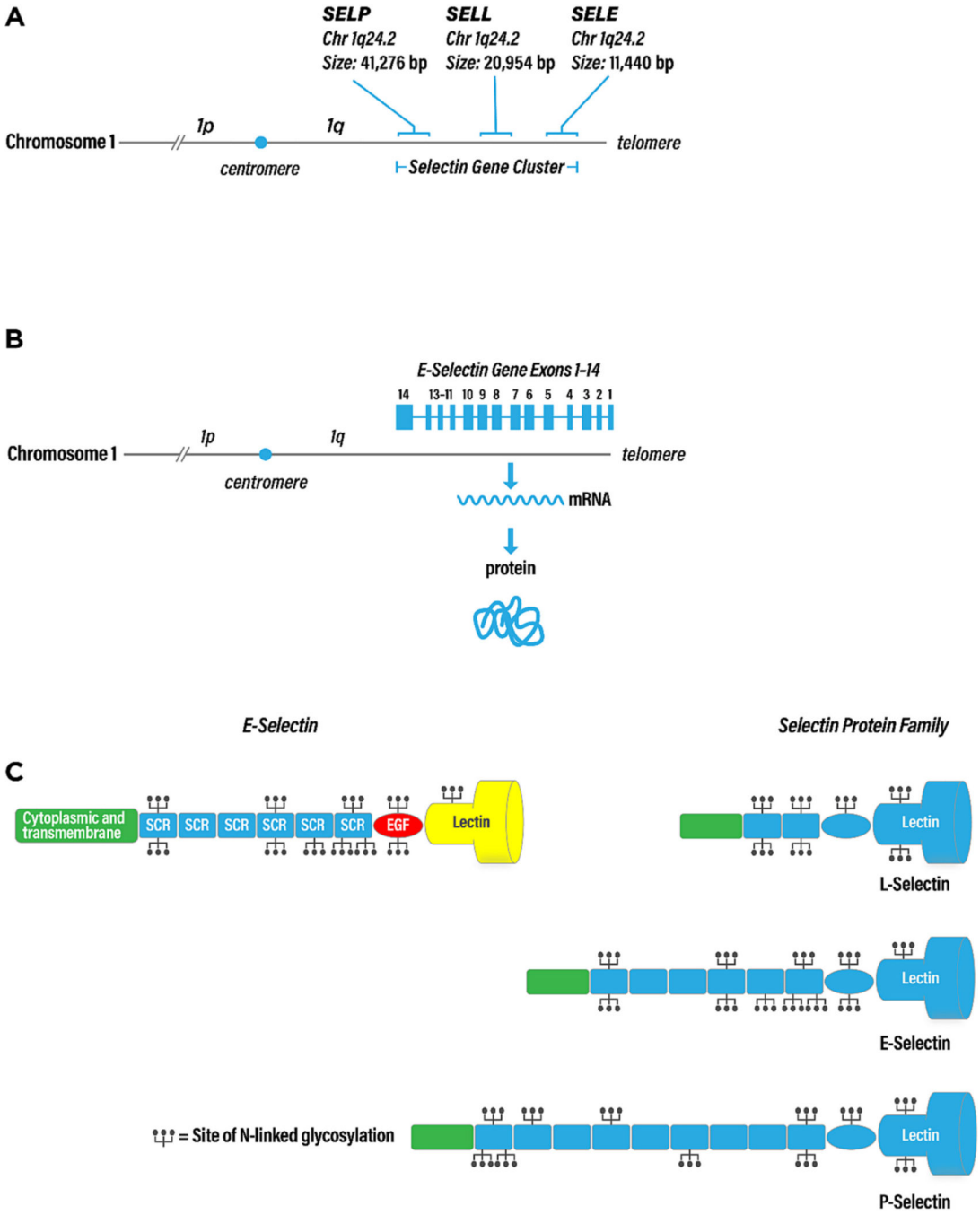

Fig. 1.

Gene organization and structure of E-selectin and related selectins [22–30]. **A**: Genes for P-selectin (*SELP*), E-selectin (*SELE*), and L-selectin (*SELL*) comprise a cluster on chromosome 1 at 1q24. **B:** The E-selectin gene contains 14 exons that encode the E-selectin protein. **C:** E-selectin is highly glycosylated, comprising lectin, epidermal growth factor-like (EGF), short consensus-repeat (SCR), and transmembrane/cytoplasmic domains (left). The lectin domain, also known as the carbohydrate recognition domain, binds to oligosaccharide

carbohydrates sialyl Le^a and sialyl Le^x. Selectin proteins vary in number of SCR domains (right).

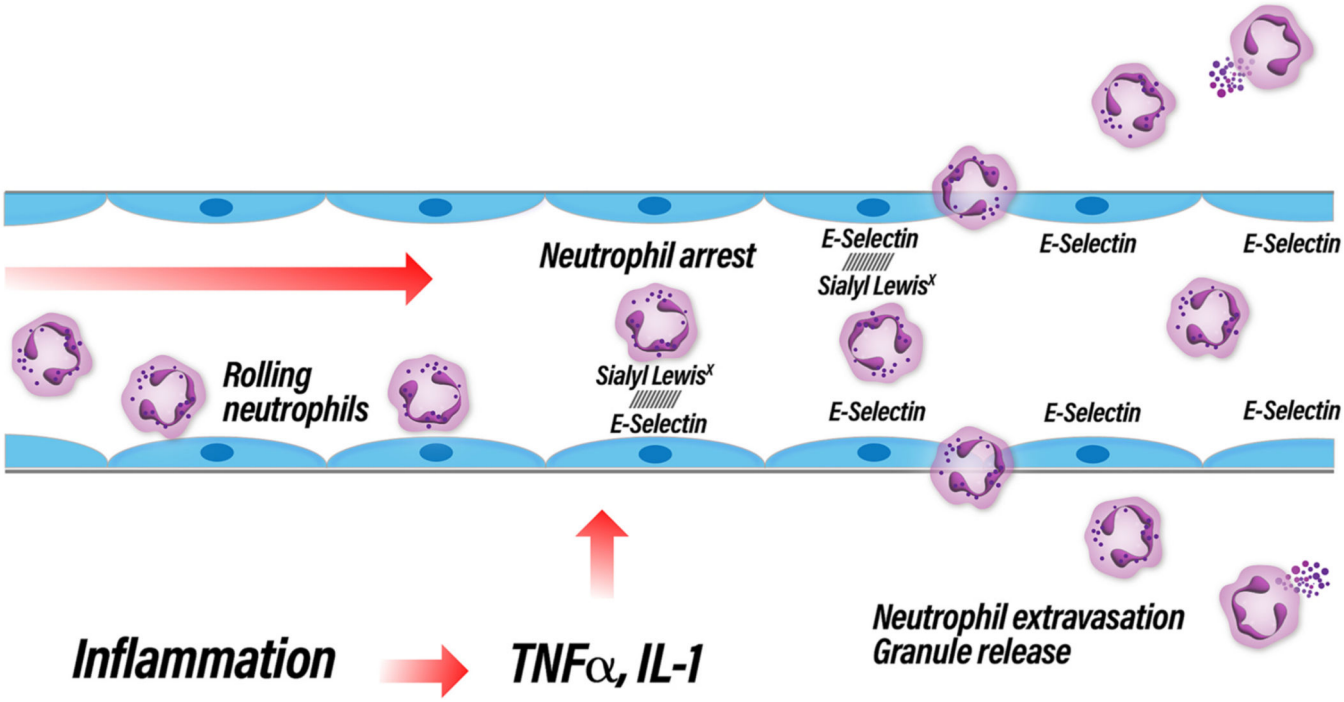

Fig. 2.

Circulating neutrophils roll on endothelium expressing E-selectin under the influence of inflammatory cytokines (TNFα and IL-1) [24]. Sialyl Lewis^x on the neutrophil surface mediates binding to endothelial cells that express E-selectin. These interactions lead to neutrophil arrest and subsequent extravasation from the bloodstream.

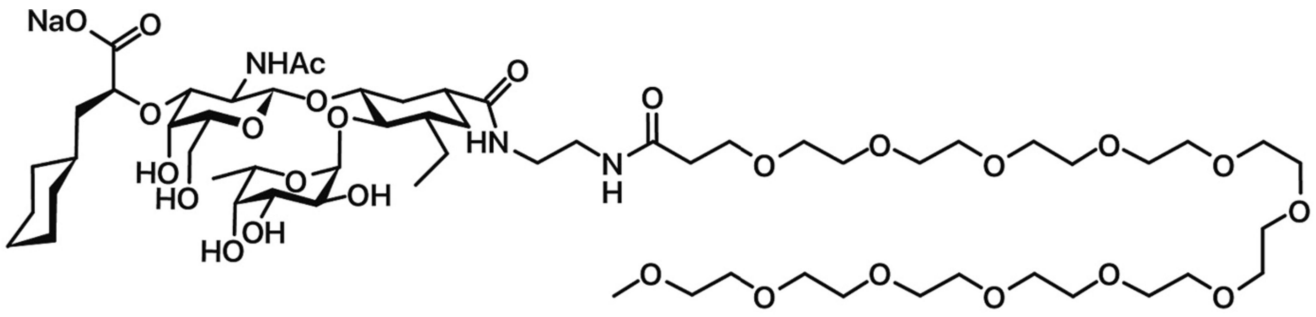

Fig. 3.

Chemical structure of glycomimetic, E-selectin antagonist, uproleselan (sodium salt), $C_{60}H_{108}N_3NaO_{27}$, molecular weight 1326.5 Da.

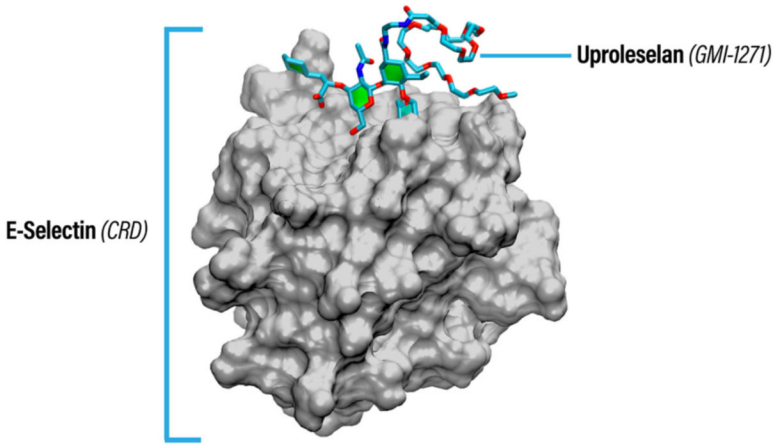

Fig. 4.

Model of uproleselan docked into the E-selectin carbohydrate-recognition domain (CRD) of E-selectin, based on the RCSB Protein Data Bank crystal structure of E-selectin [80,81].

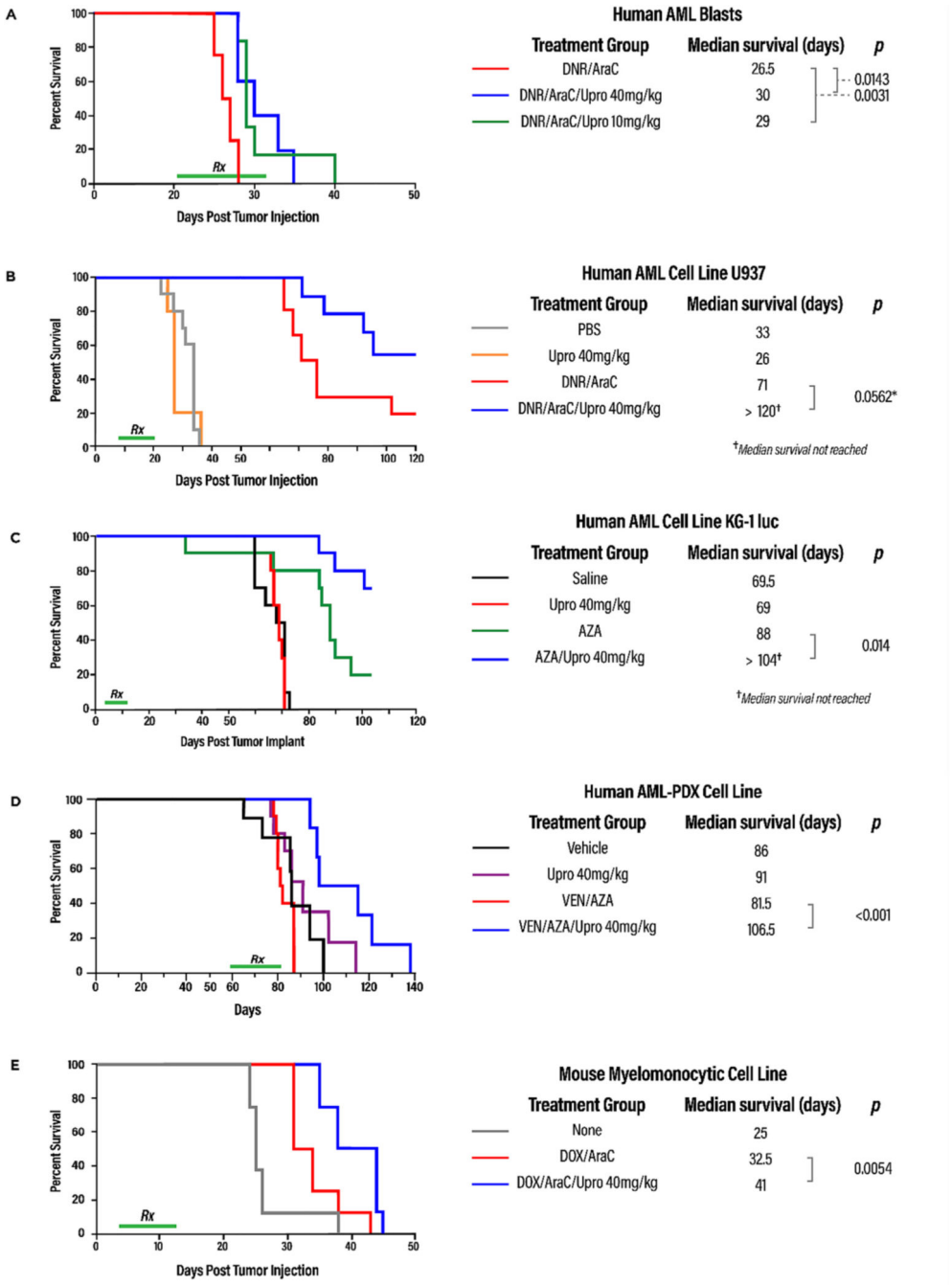

Fig. 5.

Synergy of uproleselan with chemotherapy for AML in mice. Four human AML cell lines (panels A-D) and one mouse AML cell line (panel E) were tested for response to chemotherapy +/− uproleselan in various inbred mouse lines. **A:** Human AML blasts in NOD-SCID mice, Rx with DNR/AraC +/− uproleselan 10 mg/kg or 40 mg/kg [82]. **B**: Human AML cell line U937 in NOD-SCID mice, Rx with DNR/AraC +/− uproleselan 40 mg/kg [82]. **C**: KG1-luc human AML cell line in NOD-SCID mice, Rx with AZA +/− uproleselan 40 mg/kg [83]. **D**: Human AML-PDX cells in NOD-SCID mice, Rx with

VEN/AZA +/− uproleselan 40 mg/kg [84]. **E.** Mouse monomyelocytic leukemia cells induced by retroviral *MLL-AF9*-ires-GFP cells in C57BL/6 mice, Rx DOX/AraC +/− uproleselan 40 mg/kg [18]. All *P* values reflect survival difference significance between chemotherapy with uproleselan versus chemotherapy alone.

Table 1

Evidence for potential benefits of *E*-selectin inhibition in hematologic malignancies.

Section	Observation and implication
3.2, 3.3	E-selectin mediated adhesion of AML blasts in the marrow microenvironment promotes chemotherapy resistance • E-selectin inhibition might overcome chemotherapy resistance in AML.
3.2, 3.3	Higher circulating E-selectin levels correlate with worse prognosis and greater risk of relapse in AML. • E-selectin inhibition may reverse an adverse prognostic factor in AML.
3.5, Fig. 5	Uproleselan demonstrates synergy with chemotherapy in experimental animal models of AML • Provides rationale for testing E-selectin inhibition as AML therapy in humans.
3.6	Uproleselan may improve efficacy of proteasome inhibitors (bortezomib, carfilzomib) experimental animal models of multiple myeloma. • Provides rationale for testing E-selectin inhibition as therapy for multiple myeloma in humans.
3.7	E-selectin inhibition protects against cancer therapy side effects of neutropenia and mucositis. • Suggests E-selectin inhibition might mitigate burdensome cancer therapy side effects in humans.

Table 2

Studies evaluating uproleselan pharmacokinetics.

Study	Population	Design/Dose	Phase	Subjects
GMI-271-101	Healthy adults [92]	Single-ascending dose (2, 5, and 10[a] mg/kg)	1	18
GMI-1271-102	Healthy adults [93–95]	Single- and multiple-ascending dose. Single: 2, 5, 20, & 40 mg/kg. Multiple: 10[a] & 20 mg/kg daily for 5 days.	1	22
GMI-1271-104	Healthy males [96]	Mass balance. 800 mg[a]	1	5
GMI-1271-201	Acute myeloid leukemia [91]	Multiple dose. Phase 1: 5, 10[a], and 20 mg/kg every 12 h for 8 days.[b]	1/2	59 (19)
		Phase 2: 10[a] mg/kg every 12 h for 8 days.[b]		(40)

[a]Recommended Phase 2 Dose; equivalent to 800 mg dose for 81.3 kg median body weight in GMI-1271-201 clinical trial [91,97].

[b]In combination with chemotherapy.

Table 3

Ongoing clinical trials of uproleselan in combination with chemotherapy for hematologic malignancies or hematopoietic cell transplantation.

Study (Sponsor, trial, ClinicalTrials.gov number)	Phase, design	Population	Endpoints
GlycoMimetics, Inc. GMI-1271-301 NCT03616470	Phase 3, double-blind, randomized placebo-controlled trial of MEC or FAI induction HiDAC/IDAC[a] consolidation, with uproleselan or placebo	380 adult patients with R/R AML (388 enrolled), 1:1 uproleselan: placebo, ELN 2017 risk categorization at trial entry: 41.5% adverse, 22.7% intermediate, 21.6% favorable, and 14.2% unknown risk.	Primary: Overall Survival; Key Secondaries: Severe oral mucositis rate during induction, CR rate, and remission rate (CR/CRh).
NCI-Alliance for Clinical Trials in Oncology Trial A041701 NCT03701308 NCI-2018–02130 U10CA180821	Phase 2/3 open label, randomized trial of 7 + 3 with uproleselan:7 + 3 alone	262 adult patients ≥60 years of age with untreated AML (267 enrolled), 1:1 uproleselan: placebo	Primary: Event-Free Survival.
University of California, Davis Comprehensive Cancer Center 294 NCT04964505 NCI-2021–06216 P30CA093373	Phase 1 open-label trial of AZA/VEN with uproleselan	25–31 adult patients unfit for intensive induction therapy with untreated AML (14 patients enrolled)	Primary: Safety and RP2D of uproleselan in combination with AZA/VEN
Apollomics, Inc. APL-106-02 NCT05054543	Phase 3, double-blind, randomized placebo-controlled trial of MEC induction, HiDAC/IDAC[a] consolidation, with uproleselan or placebo	140 adult patients with R/R AML, 1:1 uproleselan: placebo	Primary: Overall Survival.
John Horan, MD, Dana-Farber Cancer Institute 22–063 NCT05569512	Phase 1/2, open-label trial of uproleselan combined with high-dose busulfan	28 patients ages 12 months to 30 years undergoing HCT for chemotherapy-resistant AML	Primary: Dose-Limiting Toxicity and RP2D[b]
M.D. Anderson Cancer Center 2020–0988 NCT04848974 NCI-2021–02298	Phase 1b/2, open-label trial of uproleselan with cladribine/low dose cytarabine (LDAC) treated secondary AML	37 adult patients with treated secondary AML	Primary: Safety and RP2D
NCI PEPN2113 NCT05146739 NCI-2021-10,020 UM1CA228823	Phase 1 open-label trial of uproleselan with fludarabine/ cytarabine	18 children <18 years of age with R/R AML expressing E-selectin ligand on AML blasts	Primary: Dose-Limiting Toxicity and Pharmacokinetics

[a] HiDAC = high dose cytarabine; IDAC = intermediate dose cytarabine.

[b] RP2D = recommended Phase 2 dose.