Serpin-A1 and A3 as potential pharmacodynamic biomarkers for NOV-002, a redox modulating anticancer agent

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Abstract

NOV-002 is a formulation of disodium glutathione disulfide (GSSG) that is in Phase II clinical trials for the treatment of breast in combination with standard chemotherapeutic regimens. NOV-002 has been shown to mitigate chemotherapy-induced hematological suppression. In animal studies it was found that, when administered after chemotherapy, NOV-002 stimulated proliferation of bone marrow progenitor cells and normalized peripheral blood levels of leukocytes and platelets. NOV-002’s pharmacokinetic properties demonstrate first order absorption / elimination with a plasma half-life of ~13 mins. The redox regulation of protein thiols persist in plasma for ~4 hours. Using mass spectrometry, we identified that Serpin-A1 and A3 were S-glutathionylated following NOV-002 administration to mice. Serpin-A1 and A3 were also glutathionylated in a dose- and time-dependent S-glutathionylation following NOV-002 treatment of mouse or human plasma in vitro. There is evidence that members of the Serpin protein family can influence myeloproliferation and hematopoietic progenitor cell mobilization (Winkler et al., 2005; van Pel et al., 2006). Specifically, down regulation of serpins has been demonstrated in bone marrow during progenitor cell mobilization (van Pel et al., 2006), and this influences the marrow microenvironment and migratory behavior of hematopoietic precursor cells. Furthermore, glutathionylation of Serpins has been shown to inhibit their activity (Taygi et al., 1991 and 1992). Since our data shows that Serpins A1 and A3 are S-glutathionylated in plasma following NOV-002 treatment, there may be a mechanistic link between this effect and its in vivo myeloprotective actions. Moreover, liberation of serpins into the peripheral circulation may also provide an indication that proteolytic pathways have been activated. Since the plasma half-life of S-glutathionylated proteins is ~4 hours (Townsend et al., 2006), it may be possible to identify and develop these post-translationally modified blood proteins as pharmacodynamic biomarkers.

Background:

NOV-002: a glutathione disulfide mimetic (GSSG) is in Phase II clinical trials for the treatment of breast in combination with standard chemotherapeutic regimens. NOV-002 has been shown to mitigate chemotherapy-induced hematological suppression. In animal studies it was found that, when administered after chemotherapy, NOV-002 stimulated proliferation of bone marrow progenitor cells and normalized peripheral blood levels of leukocytes and platelets. NOV-002’s pharmacokinetic properties demonstrate first order absorption / elimination with a plasma half-life of ~13 mins. The redox regulation of protein thiols persist in plasma for ~4 hours. Using mass spectrometry, we identified that Serpin-A1 and A3 were S-glutathionylated following NOV-002 administration to mice. Serpin-A1 and A3 were also glutathionylated in a dose- and time-dependent S-glutathionylation following NOV-002 treatment of mouse or human plasma in vitro. There is evidence that members of the Serpin protein family can influence myeloproliferation and hematopoietic progenitor cell mobilization (Winkler et al., 2005; van Pel et al., 2006). Specifically, down regulation of serpins has been demonstrated in bone marrow during progenitor cell mobilization (van Pel et al., 2006), and this influences the marrow microenvironment and migratory behavior of hematopoietic precursor cells. Furthermore, glutathionylation of Serpins has been shown to inhibit their activity (Taygi et al., 1991 and 1992). Since our data shows that Serpins A1 and A3 are S-glutathionylated in plasma following NOV-002 treatment, there may be a mechanistic link between this effect and its in vivo myeloprotective actions. Moreover, liberation of serpins into the peripheral circulation may also provide an indication that proteolytic pathways have been activated. Since the plasma half-life of S-glutathionylated proteins is ~4 hours (Townsend et al., 2006), it may be possible to identify and develop these post-translationally modified blood proteins as pharmacodynamic biomarkers.

Conclusions:

- NOV-002 oxidative signaling results in S-glutathionylation of Serpins A1 and A3 in mouse (in vivo) and human (in vitro) plasma
- Serpin S-glutathionylation could serve as a pharmacodynamic biomarker for NOV-002 bioactivity
- Since glutathionylation is known to inhibit Serpin function, this effect of NOV-002 could contribute to its ability to reverse cyclophosphamide-induced hematological suppression