421

Targeting colony stimulating factor- 1 receptor (CSF-1R) with SNDX-6352, a novel anti-CSF-1R targeted antibody

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BACKGROUND

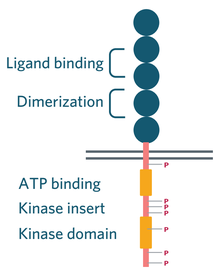
CSF-1R is expressed on cells of the mononuclear phagocyte lineage including immunosuppressive macrophages that accumulate within the tumor microenvironment.

These tumor-associated macrophages (TAMs) are believed to play a key role in inhibiting anti-tumor T cell immune responses while promoting tumor progression.[1] High levels of TAMs have been shown to correlate with poor prognosis for certain cancers, and preclinical studies have demonstrated that inhibition of TAMs can enhance anti-tumor immune responses.[2,3] SNDX-6352 is a humanized IgG4P monoclonal antibody with high affinity against CSF-1R that is under investigation for the treatment of neoplastic diseases.

SNDX-6352 ANTIBODY SUMMARY

Figure 1. **SNDX-6352 antibody summary**

CSF-1R



- **2 ligands: CSF-1, IL-34**
- **Tissue expression**
  - Mononuclear phagocytic cells (monocytes), tissue macrophages, Kupffer cells, Langerhans cells, microglial cells, osteoclasts, hematopoietic precursors, and trophoblasts.
- **Function**
  - Proliferation, survival, differentiation, chemotaxis of mononuclear phagocytic cells and their precursor.
- **Macrophages**
  - Important roles in tissue development/ homeostasis, immune responses.
  - Key roles in cancer and fibrosis.

SNDX-6352

Antibody Properties

- High affinity, humanized IgG4P* (K_D = 4-8 pM).
- Demonstrated binding to CSF-1R variants carrying 4 different SNPs/mutations (VG2G,A245S, P247H, V279M).
- Blocks binding of both CSF-1 and IL-34.
- Potent inhibitor of ligand-induced monocyte activation.
- Cross-reacts with cynomolgus monkey CSF-1R.
  - Does not cross-react with rodent CSF-1R.
  - Rodent surrogate generated (Ab535).
- No evidence of antibody-mediated receptor internalization or activation.

*High affinity, humanized IgG4P contains an S228P mutation to stabilize the molecule and prevent Fab arm exchange.

BINDING

In vitro studies using the Biacore assay have demonstrated that SNDX-6352 binds with high affinity to human CSF-1R (KD 4-8 pM, Fc-tagged construct) and cross-reacts with cynomolgus monkey CSF-1R but not rodent CSF-1R.

Table 1. Binding of SNDX-6352 to Recombinant Human CSF-1R

SNDX-6352	k_a (M-1s-1)	K_d (s-1)	k_D (M)	KD (pM)
Anti-Hu F(ab)'2 capture				
Hu CSF-1R-Fc	3.15E+06	2.31E-05	7.33E-12	7.3
	3.11E+06	1.27E-05	4.08E-12	4.1
mean				5.7
Hu CSF-1R-His	7.41E+05	1.06E-03	1.43E-09	1430
	7.20E+05	1.04E-03	1.44E-09	1440
mean				1435

Table 2. Specificity of SNDX-6352 for Non-rodent Species

Anti-Hu Fc Capture	k_a (M-1s-1)	K_d (s-1)	K_D (M)	KD (nM)
Hu CSF-1R-His	9.85E+05	1.27E-03	1.29E-09	1.29
	9.31E+05	1.26E-03	1.35E-09	1.35
mean				1.32
Cyno CSF-1R-His	1.62E+06	2.26E-02	1.40E-08	14.0
	1.70E+06	2.16E-02	1.27E-08	12.7
mean				13.4
Mouse CSF-1R-His	No binding			

CELL BIOLOGY

SNDX-6352 has been shown to potently inhibit both CSF-1– and IL-34–induced MCP-1 release from human monocytes (IC_{50} = 0.27 nM or 39.9 ng/mL; IC_{50} = 0.1 nM or 15.09 ng/mL, respectively) and completely inhibits the viability of macrophages during the CSF-1–mediated differentiation process in vitro (IC_{50} = 0.455 nM).

Figure 2A. **SNDX-6352 effect on CSF-1–dependent MCP-1 release**

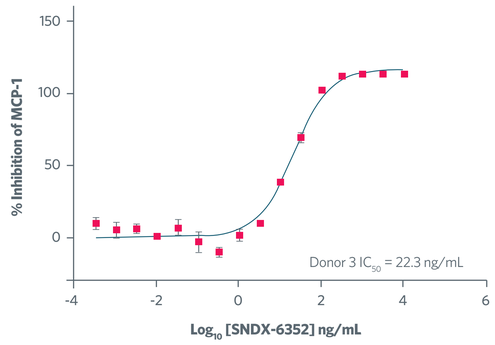
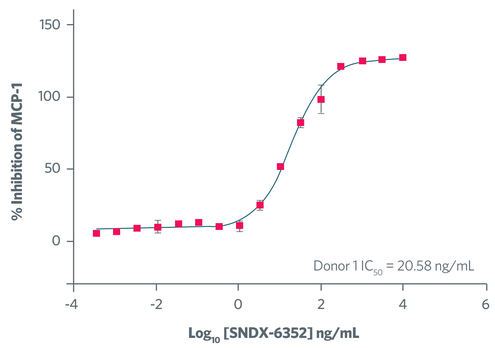


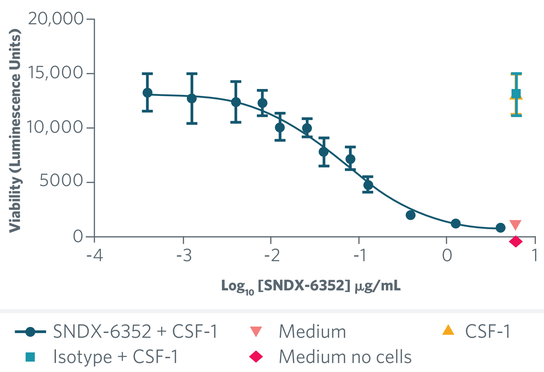
Figure 2B. **SNDX-6352 effect on IL-34–dependent MCP-1 release**



Incubated with 100 ng/mL	IC_{50} (ng/mL)					IC_{50} (nM)
	Donor 1	Donor 2	Donor 3	Donor 4	Mean ± SE	Mean ± SE
Recombinant human CSF-1	80.6	42.2	22.3	14.4	39.9 ± 14.8	0.27 ± 0.10
Recombinant human IL-34	20.58	9.59			15.09 ± 5.51	0.10 ± 0.04

SNDX-6352 inhibits CSF-1– and IL-34–dependent MCP-1 release from primary human monocytes. Primary human monocytes were incubated with 100 ng/mL recombinant human CSF-1 (**2A**) or IL-34 (**2B**) and a dose titration of SNDX-6352 for 24 hours. Secreted MCP-1 was measured by ELISA. Graphs show percentage inhibition of MCP-1 production compared with the CSF-1– or IL-34–only control.

Figure 3. **CSF-1 differentiated macrophages**



SNDX-6352 inhibits the viability of macrophages during the CSF-1–mediated differentiation process in vitro. Human monocytes were incubated with CSF-1 with or without SNDX-6352 for 6 days. Cell viability was determined with CellTiter-Glo®.

NON-CLINICAL DEVELOPMENT

Pharmacologic SNDX-6352–related increases in CSF-1 and decreases in non-classical (CD14+CD16+) monocytes and markers of bone formation and resorption (data not shown) were observed during the treatment phase and were rapidly reversed upon SNDX-6352 clearance. Changes in bone markers were not associated with histologic changes or changes in bone densitometry.

Figure 4A. **Target mediated drug disposition**

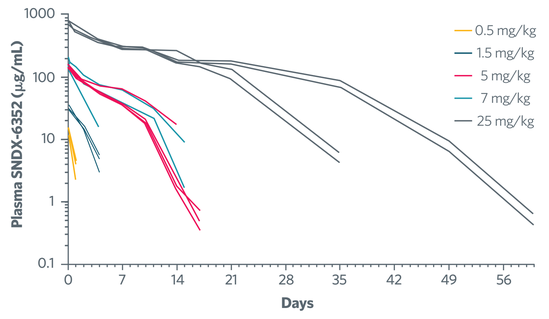


Figure 4B. **Target occupancy**

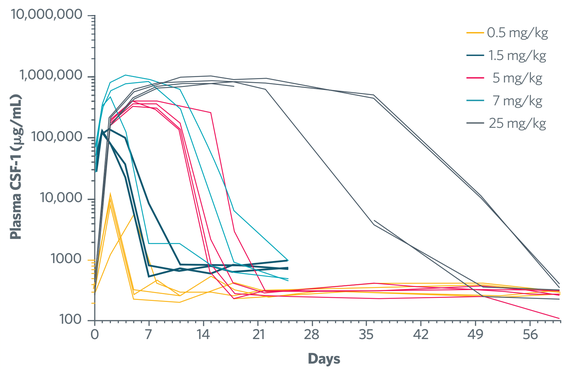
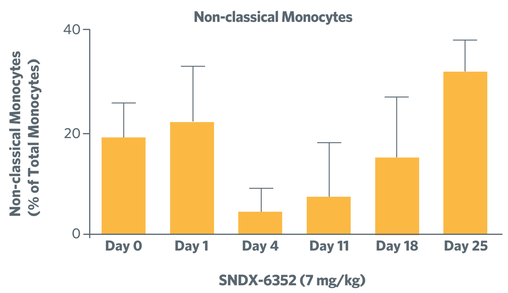
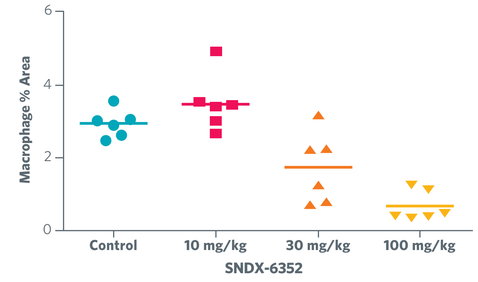


Figure 4C. **Target engagement**



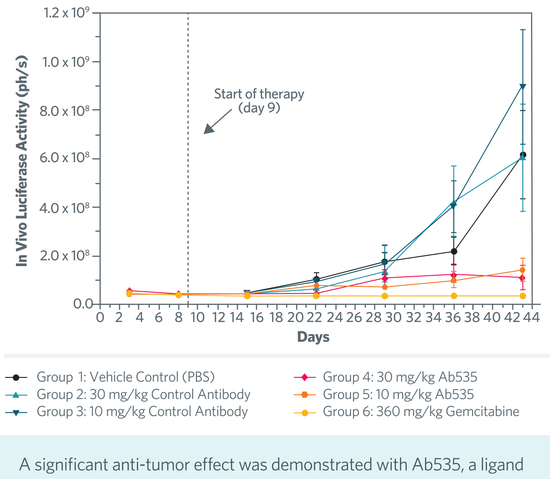
PK/PD of SNDX-6352 in primates. **4A:** PK of SNDX-6352 changes with dose due to target-mediated clearance. **4B:** Sustained increase in CSF-1 levels following single dose of SNDX-6352 ≥5 mg/kg indicates full target occupancy. **4C:** Sustained and specific effect on circulating non-classical monocytes following single dose of 7 mg/kg SNDX-6352.

Figure 5. **SNDX-6352 effect on tissue macrophage numbers**



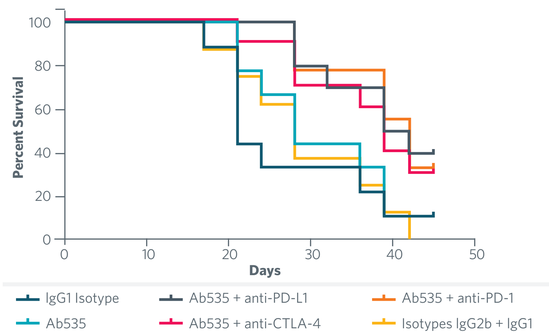
Depletion of tissue macrophages resulted from effective CSF-1R inhibition in a non-human primate study.

Figure 6. **Effect of surrogate blocking antibody Ab535 in a prostate cancer mouse model**



A significant anti-tumor effect was demonstrated with Ab535, a ligand blocking anti-mouse CSF-1R antibody in a PC-3 prostate cancer model. 2 × 10^6 PC-3-LN prostate cancer cells were orthotopically implanted. Ab535 was administered 3 times per week until the end of study. Gemcitabine was used as a positive control.

Figure 7. **Effect of surrogate blocking antibody Ab535 combined with checkpoint inhibitors on survival**



Combination of Ab535 with anti-PD-1, anti-PD-L1, and anti-CTLA-4 resulted in an increased overall survival compared with the monotherapy groups at the study termination point in the syngeneic MC-38 mouse tumor model.

CONCLUSIONS

- SNDX-6352 is a novel, high affinity humanized, IgG4P anti-CSF-1R antibody that blocks CSF-1R.
- Strong preclinical evidence of anti-tumor and anti-metastatic efficacy or effects (breast and prostate).
- Additional benefit of combining CSF-1R and PD-1/CTLA4 blockade demonstrated in pancreatic adenocarcinoma model.
- Excellent non-clinical PK and safety profile.
- First-in-human studies have been initiated.

References

1. Noy R & Pollard JW. *Immunity*. 2014:41;49-61.
2. Ries CH, et al. *Cancer Cell*. 2014:25:846-859.
3. Zhu Y, et al. *Cancer Res*. 2014:74;5057-5069.

Acknowledgments

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