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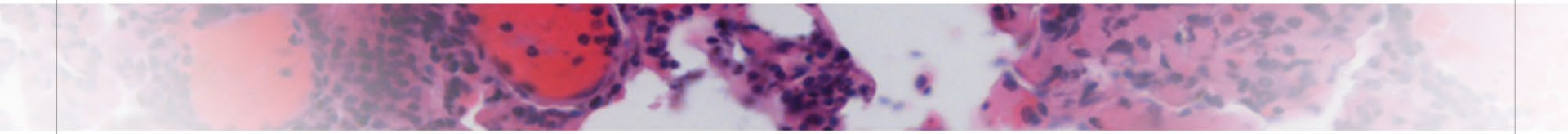

Discovery of INCA033989, a Monoclonal Antibody That Selectively Antagonizes Mutant Calreticulin Oncogenic Function in Myeloproliferative Neoplasms

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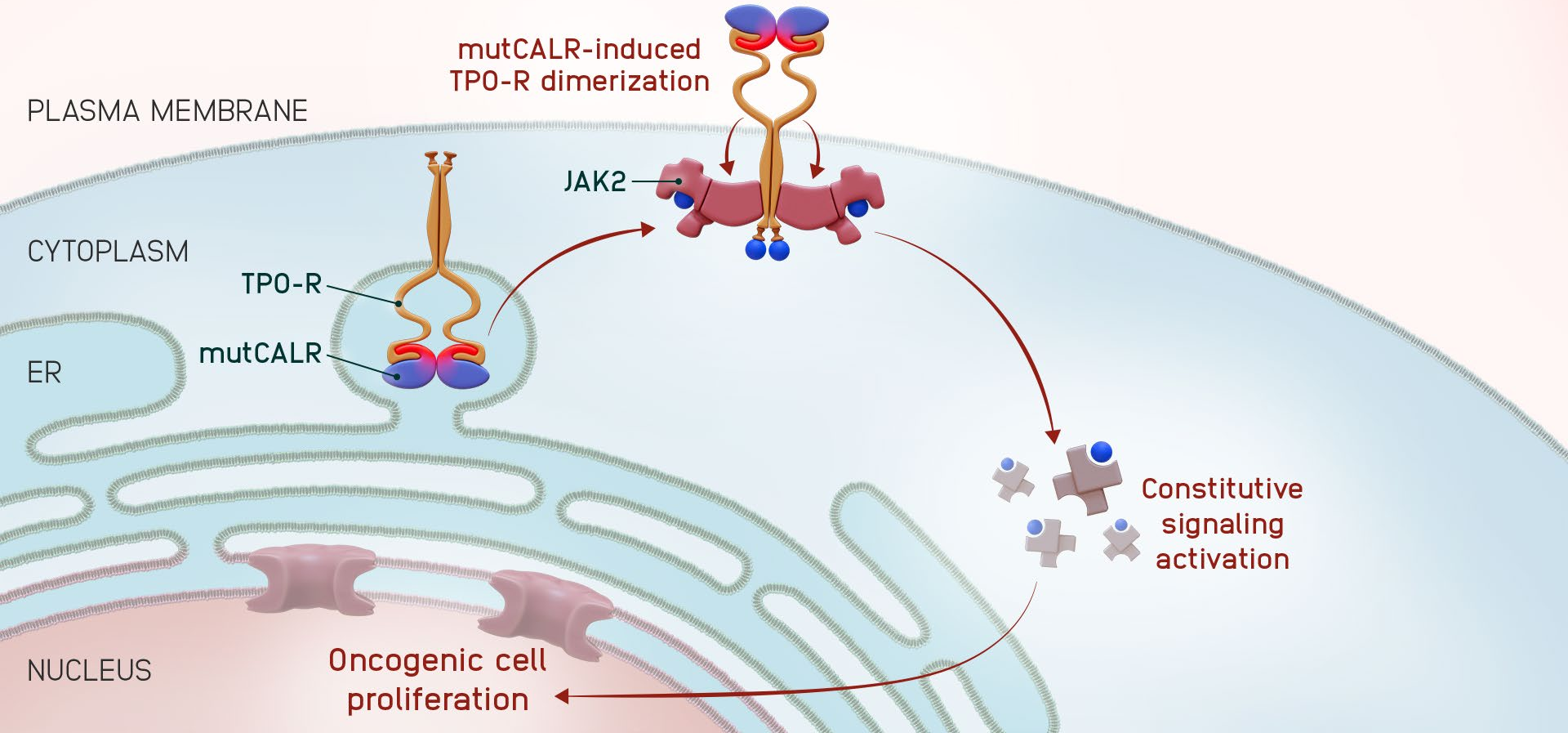
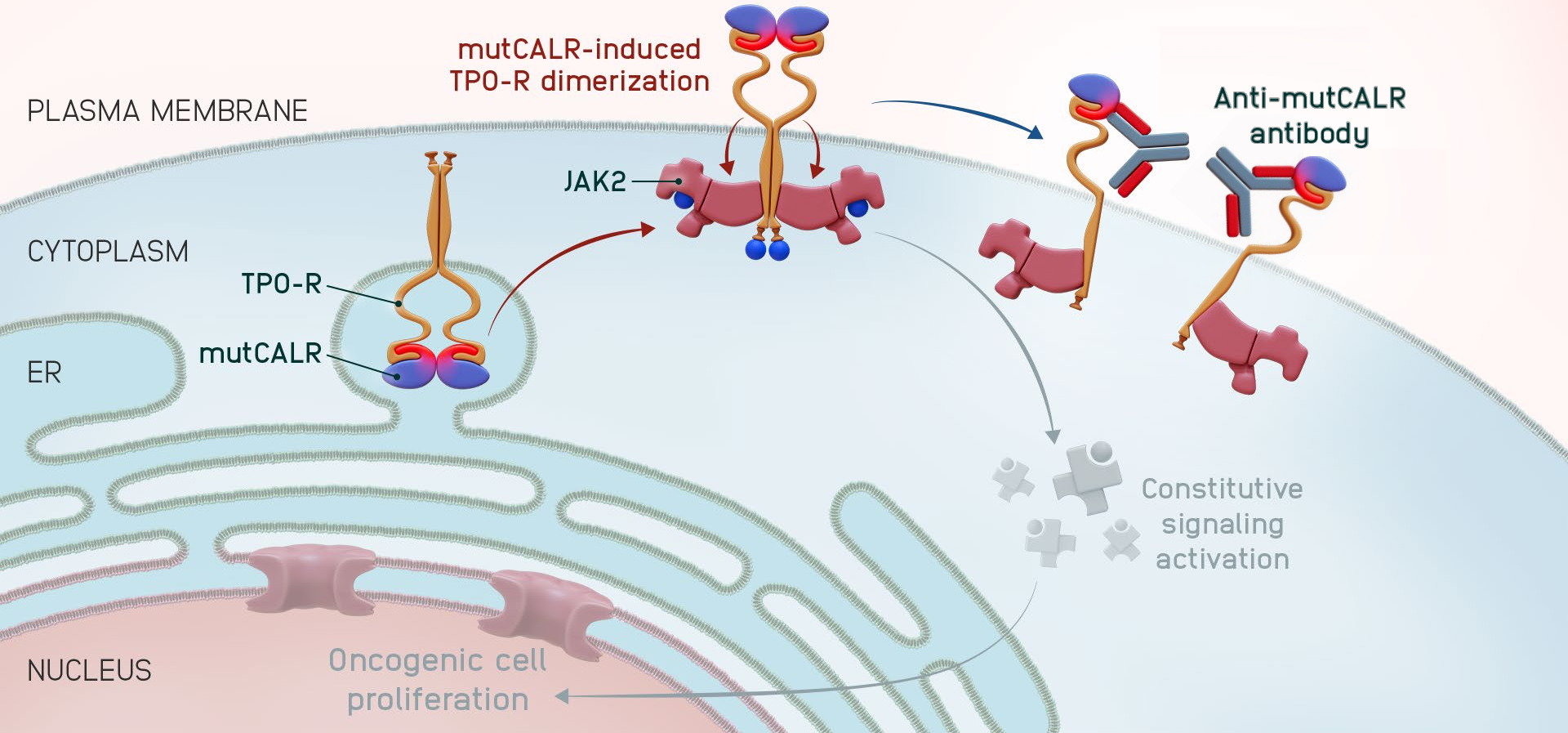
Mutant calreticulin (mutCALR) induces oncogenic cell proliferation

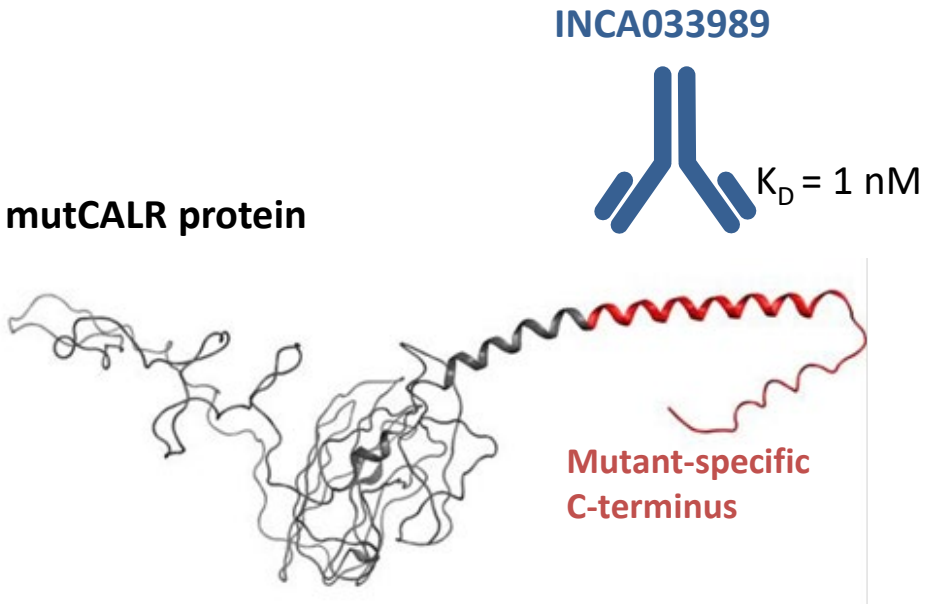


Anti-mutCALR antibody selectivity inhibits oncogenic cell proliferation



INCA033989: a mutCALR-specific monoclonal antibody

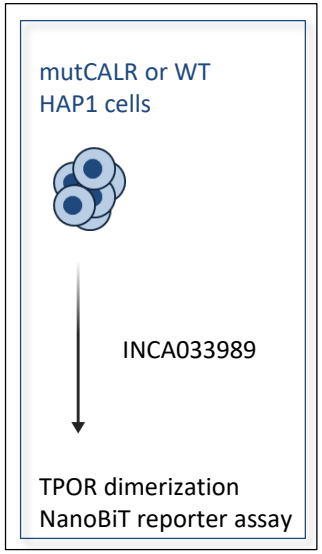
- Fully human IgG1
- Fc-silent
- Selective binding to mutCALR
- Antagonizes mutCALR-induced signaling and oncogenic function

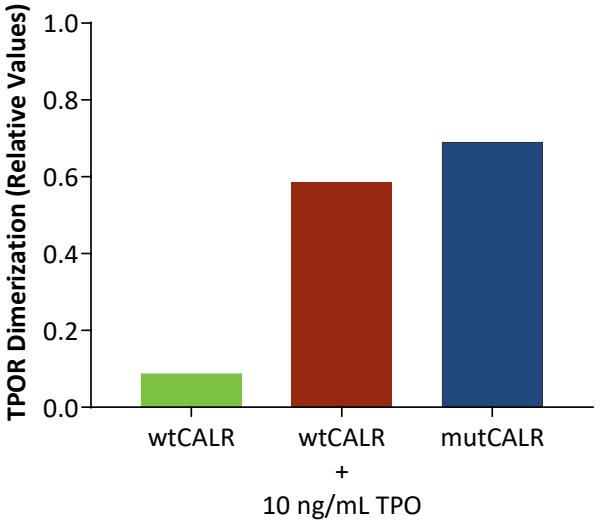


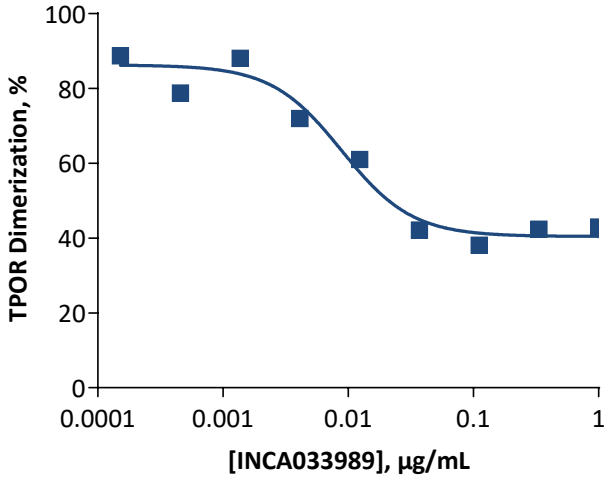
Structure generated with RaptorX (Toyota Technological Institute at Chicago, IL, USA).

IgG, immunoglobulin G; Fc, fragment crystallizable; K_D, equilibrium dissociation constant.

INCA033989 reverts mutCALR-induced TPOR dimerization

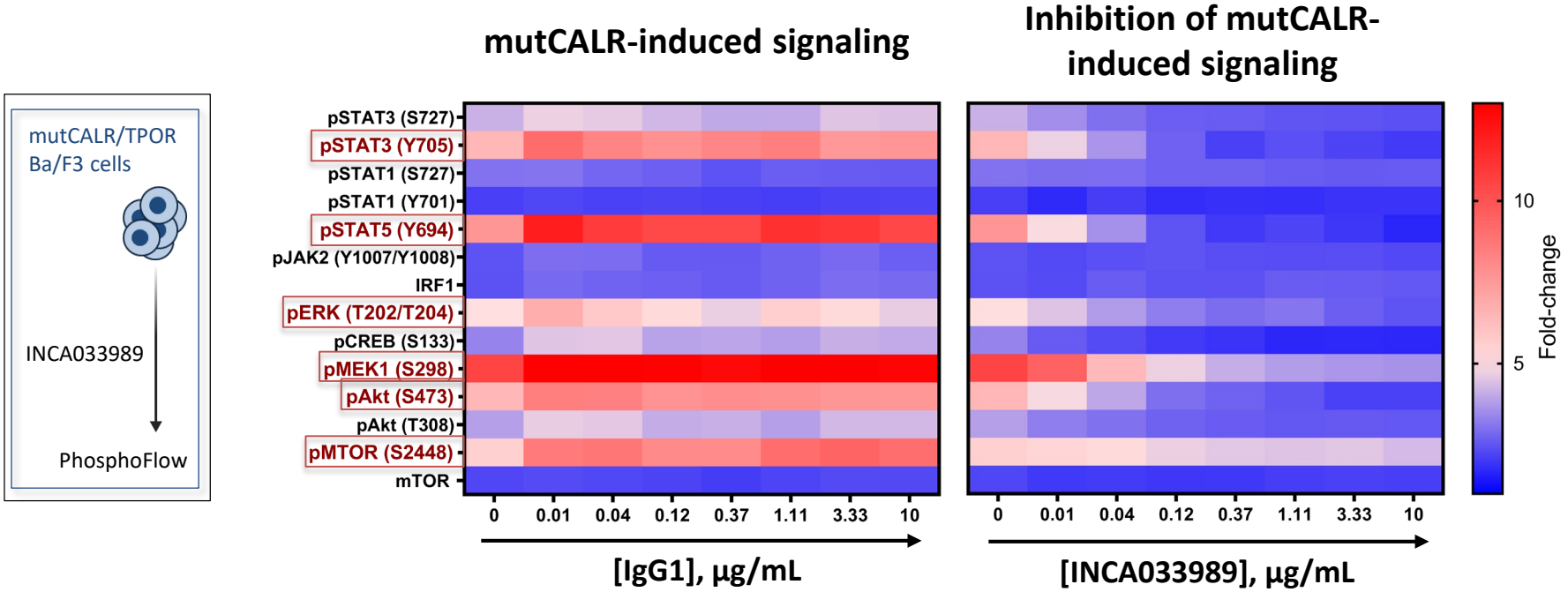






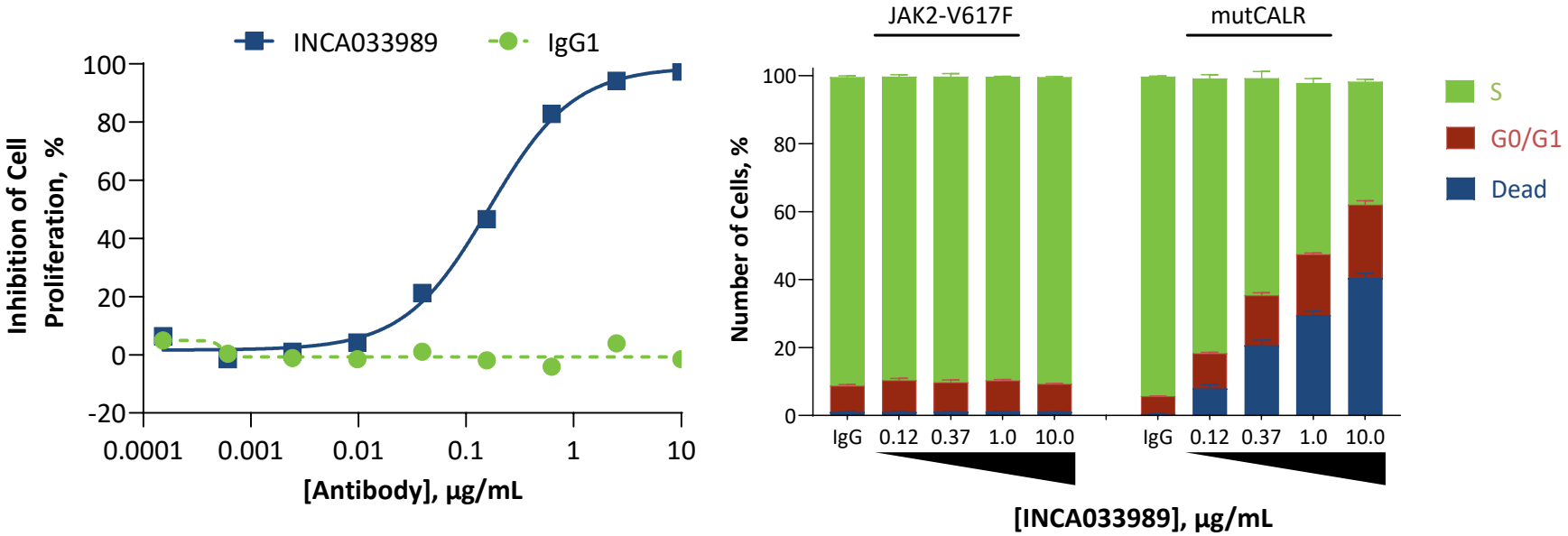
NanoBiT, nanoluciferase binary technology; TPO, thrombopoietin; WT, wild-type.

INCA033989 inhibits mutCALR-induced oncogenic signaling

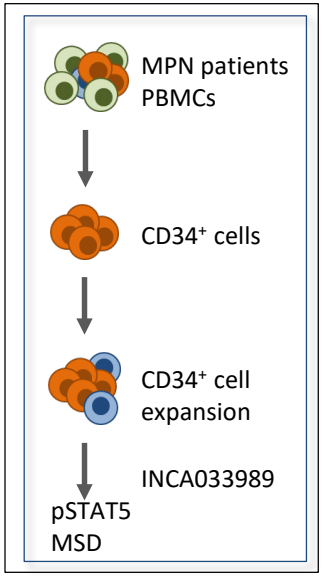


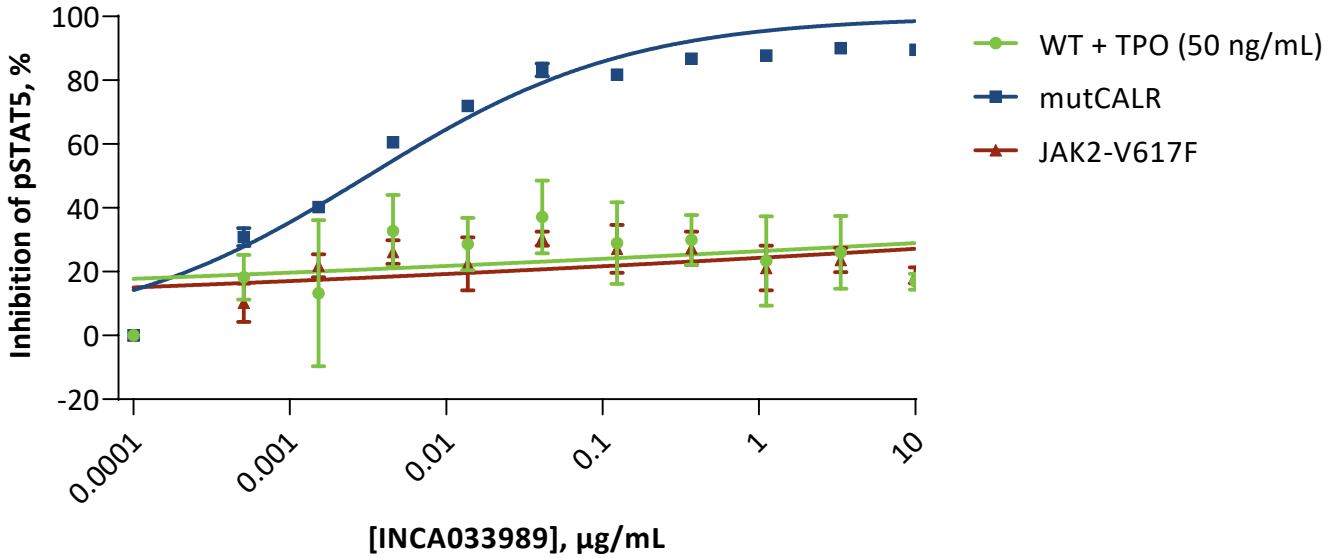
Bianca Lima Ferreira, Ian Hitchcock. York Biomedical Research Institute, University of York.

INCA033989 selectively inhibits cell proliferation and induces death of mutCALR^{+} cells



INCA033989 selectively inhibits pSTAT5 in primary CD34+ mutCALR+ cells

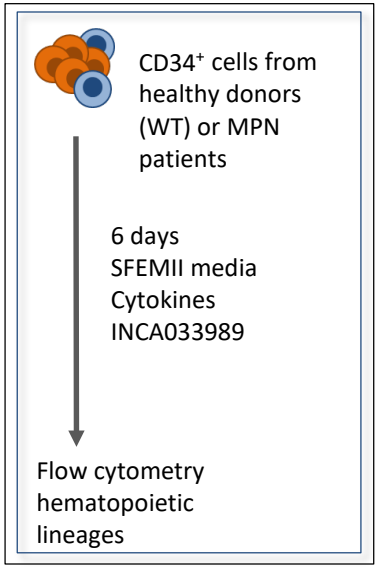


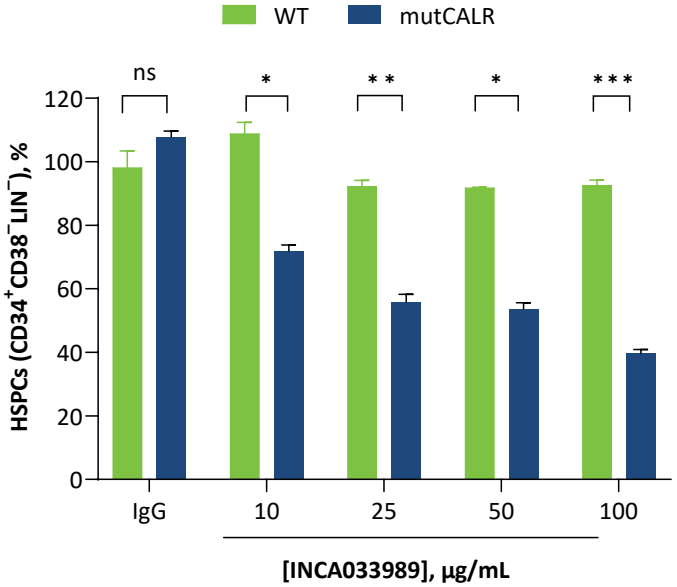


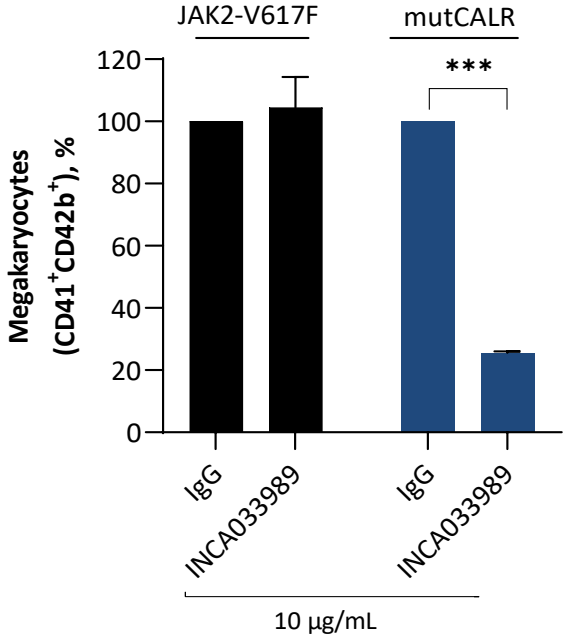
Error bars correspond to SEM and are within the symbol size where not visible.

JAK2, Janus kinase 2; MPN, myeloproliferative neoplasm; PBMC, peripheral blood mononuclear cell; SEM, standard error of the mean.

INCA033989 selectively inhibits the proliferation of mutCALR^{+} HSPCs

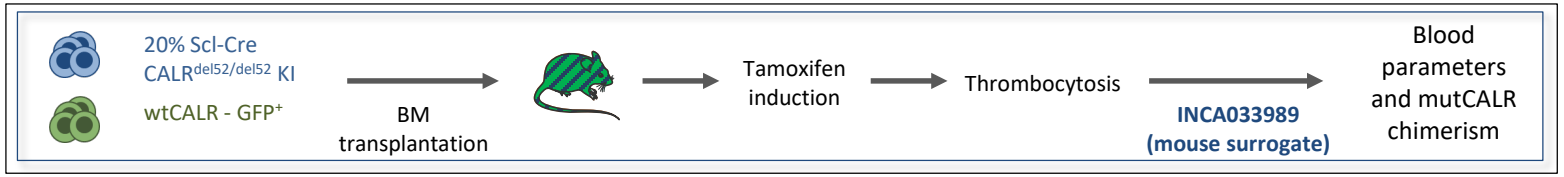


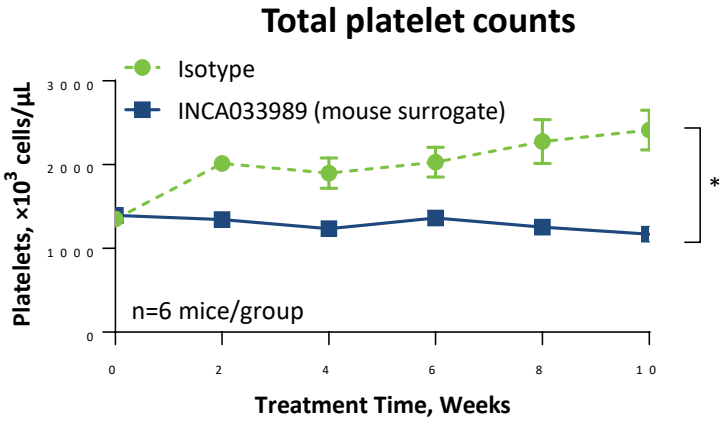


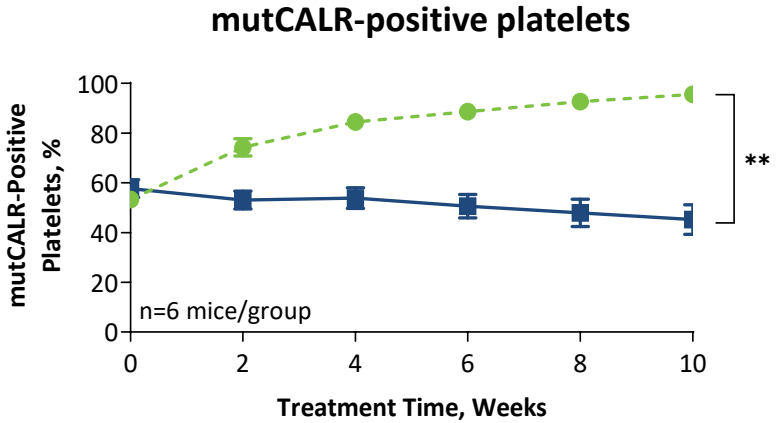


*P<0.01; **P<0.001; ***P<0.0001.
HSPC, hematopoietic stem progenitor cells; ns, not significant.

INCA033989 surrogate restores hematologic and molecular responses in a murine model of ET







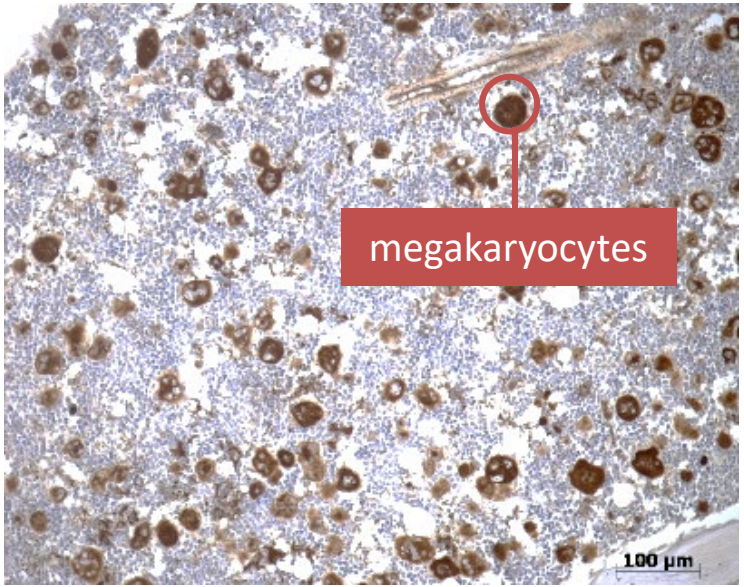
*P<0.001; **P<0.0001.

BM, bone marrow; ET, essential thrombocythemia.

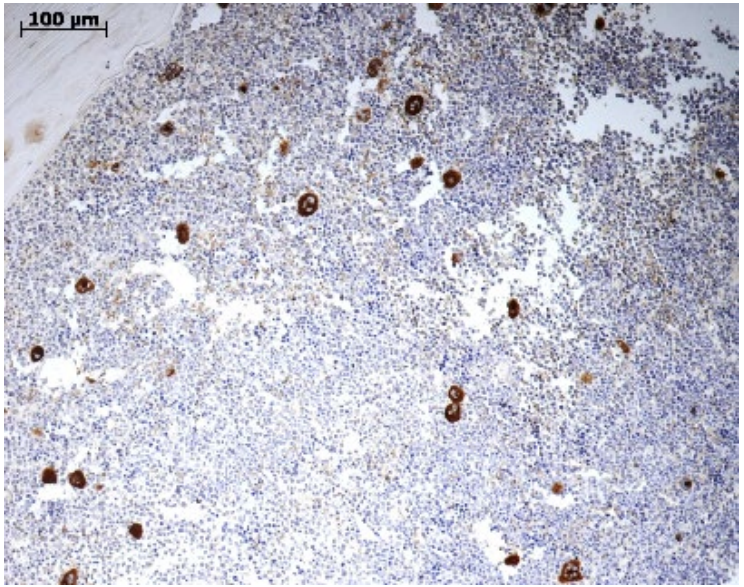
Caroline Marty, Elodie Rosa, Maxime Evrard, William Vainchenker, Isabelle Plo. Gustave Roussy Institute, INSERM, Université Paris-Saclay.

INCA033989 surrogate treatment re-establishes normal megakaryopoiesis

Isotype



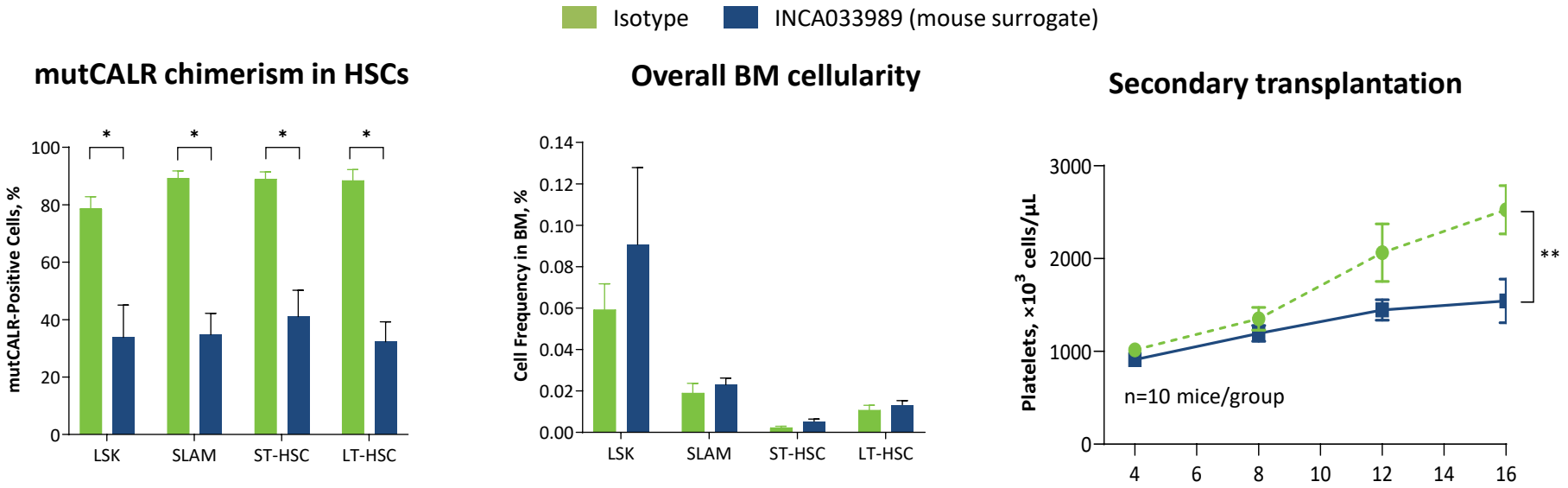
INCA033989 (mouse surrogate)



Megakaryocytes stained with anti–von Willebrand factor antibody.

Caroline Marty, Elodie Rosa, Maxime Evrard, William Vainchenker, Isabelle Plo. Gustave Roussy Institute, INSERM, Université Paris-Saclay.

INCA033989 surrogate selectively targets mutCALR disease–initiating clones



*P<0.001; **P<0.0001.

LSK, Lin⁻Sca⁺Kit⁺; LT-HSC, long-term hematopoietic stem cell; SLAM, signaling lymphocyte activation molecule; ST-HSC, short-term hematopoietic stem cell.

Caroline Marty, Elodie Rosa, Maxime Evrard, William Vainchenker, Isabelle Plo. Gustave Roussy Institute, INSERM, Université Paris-Saclay.

Summary

- INCA033989 is a potent antagonist of mutant calreticulin function:
  - Selective inhibition of JAK/STAT signaling and proliferation of *CALR*-mutated stem progenitor cells
  - Potential to alter the course of disease in ET and MF patients by targeting disease-initiating (stem) cells
  - May mitigate clinical adverse events associated with broad inhibition of JAK/STAT in non-mutated cells
- These data provide strong rationale for the clinical investigation of INCA033989 in MF and ET patients with *CALR* mutations
- A phase 1 study of INCA033989 is planned to initiate in 2023

MF, myelofibrosis.

Acknowledgments

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- Ian Hitchcock

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