Supplementary Material

Drug repurposing: Ibrutinib exhibits immunosuppressive potential in organ transplantation

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Abbreviations

PBMCs: Peripheral blood mononuclear cells

POD: Post operation days

JAK: Janus kinases

Syk: Spleen Tyrosine Kinase

PKC: Protein kinase C

IFN-γ: Interferon gamma

TNF-α: Tumor necrosis factor alpha

IL-2: Interleukin-2

IL-4: Interleukin-4

IL-6: Interleukin-6

BTK: Bruton's tyrosine kinase

ITK: IL-2 inducible T cell kinase

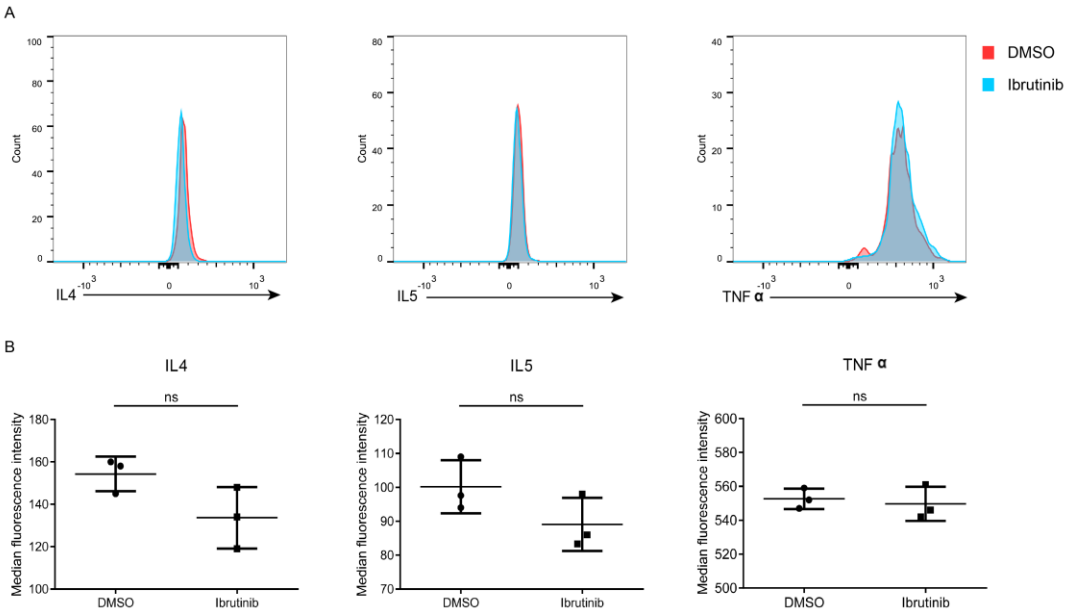
Th cells: helper T cells

OCT: Optimal Cutting Temperature

CFSE: carboxyfluorescein succinimidyl amino ester

Supplementary Table 1. Kinase inhibitors as potential immunosuppressants.

Kinases	Inhibitors	Therapeutic Effects	Adverse Effects
Janus kinases (JAKs)	Tofacitinib [1]	Prevent biopsy-proven acute rejection (BPAR) in kidney transplantation	Infection, post-transplant diabetes and malignancy
	Ruxolitinib phosphate (Jakafi®) [2]	Therapeutic effects in patients with an inadequate response to or intolerance of hydroxyurea and in patients after hematopoietic stem cell transplant	Not investigated in solid organ transplantation
	PNU156804[3, 4]	Prolong graft survival of heart allografts	Better effects in combination therapy
Spleen tyrosine kinase (Syk) [5] [22]	Fostamatinib [6]	Phase 1 clinical trial: prevent chronic graft vs. host disease by reducing $CD8^+$ T cells, renal monocyte chemo-attractant protein-1 (MCP-1) and IL-1β	Hypertension, diarrhea, neutropenia and increases in hepatic enzyme levels [7]
	CC0482417 [8]	Reduction of allograft rejection and histological damage after rat kidney transplantation; attenuated acute tubular necrosis, infiltration of macrophages and neutrophils and thrombosis of peritubular capillaries	Failure to prevent T-cell infiltration and activation within the allograft
Protein kinase C (PKC)	Sotrastaurin (AEB071) [9]	T/B cell activation and proliferation inhibition	Severe adverse effects
Receptor tyrosine kinases (PDGFR-α/β and VEGF receptors)	Sunitinib	Prevention of chronic rejections after experimental kidney transplantation [10]	Nephrotic syndrome [11]



Supplementary figure 1. Influence of ibrutinib on cytokines secretion. (A) Representative result of cytokines (IL-4, IL-5 and TNF-α) secreted from PBMCs (POD 14) after treatment with ibrutinib (final conc. 1μM). (B) Statistics of MFI of cytokines (IL-4, IL-5 and TNF-α) secreted from PBMCs (POD 14) after treatment with ibrutinib (final conc. 1 μM). Datas are representative of at least three independent experiments (mean±SEM). (*p < 0.05, **p < 0.01, ***p < 0.001 by Student's *t* test.)

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