MEDICAL COLLEGE OF WISCONSIN
Office of TECHNOLOGY DEVELOPMENT
Patents to Patients®

Next-Generation JAK2-Inhibitors Targeting Wild-Type Jak2 and Depleting Androgen Receptor Levels for Prostate Cancer Therapy

Exclusive Licensing Opportunity

MCW 2068

Problem Description

Men diagnosed with prostate cancer (PC) at an advanced stage or experiencing tumor recurrence after surgery require androgen deprivation (ADT) (achieved by GnRH agonist/antagonist or anti-androgens) to inhibit the androgen receptor (AR) transcription factor. A major challenge in the clinical management in this population is progression to lethal castrate-resistant PC (CRPC) despite the ADT. CRPC is consistently caused by an acquired ability of tumors to express AR and its constitutively active splice variants (AR-Vs) driving ongoing AR activity that promoting PC tumor growth and metastasis, and ultimately causing patient death.

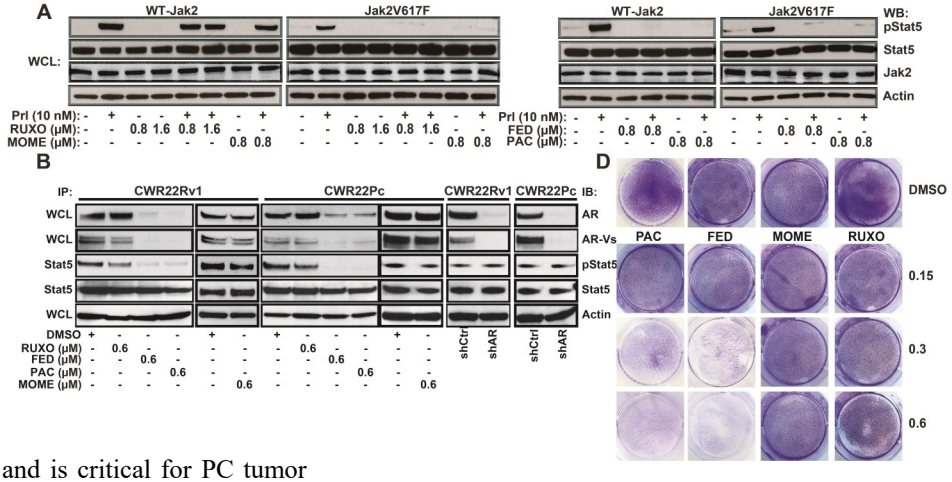

Figure: The efficacy of Jak2 inhibitors PAC and FED compared to RUXO or MOME in suppressing A) Wt-Jak2 induced activation of Stat5 in a cell-based assay, B) AR protein and mRNA (not shown) levels and C) viability of PC cells.

Jak2-Stat5 signaling sustains PC cell viability and is critical for PC tumor growth. Also, Stat5 activation in PC at the time of diagnosis predicts early PC recurrence. Our investigation of the molecular targets downstream of Jak2-Stat5 signaling show that the AR gene as a critical target, and the Jak2 -Stat5 pathway suppression represents an effective strategy to deplete diverse AR and AR-V species and thereby control of PCRPC growth.

Problem Solved

We have demonstrated that the next-generation Type I Jak2 inhibitors, Pacritinib (PAC) and Fedratinib (FED) (among others), target wild-type Jak2 in cell-based assays and suppress AR mRNA and protein levels in PC. Importantly, Wt-Jak2 targeting Jak2-inhibitors induce robust death of PC cells, in PC xenograft tumors and clinical patient-derived PCs *ex vivo* in explant cultures. In contrast, the first-generation Jak2-inhibitor, Ruxolitinib (RUXO), which failed in clinical trials in PC, displayed no suppression of WtJak2-Stat5-AR axis in PC or PC cell viability.

Application

A new class of androgen receptor antagonists for prostate cancer therapy.

Key Advantages

- **Represents a significant market opportunity**
- **Depletion of Androgen Receptor (AR) levels in PC provides a therapy option for hormone-sensitive and hormone-resistant prostate cancer.**

Stage of Development:
Phase II trial

Intellectual Property Status:
PCT Application filed
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