A potent and selective cFMS inhibitor regulating the tumor microenvironment leading to tumor growth inhibition


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Introduction

- Interactions between tumor cells, stromal cells, macrophages and the extracellular matrix are pivotal to the processes of tumorigenesis, metastasis, and neovascularization.
- Macrophages within the tumor microenvironment may facilitate cancer progression, making them intriguing targets for therapy.
- Colony stimulating factor 1 (CSF-1) and its receptor, cFMS or CSF1R, play a central role in the development of mononuclear phagocytes, recruitment of macrophages to tumors, and differentiation and function of osteoclasts.

In this study, we investigate in more detail the molecular mechanisms involved in cFMS inhibition on modulation of tumor-associated macrophage function and tumor growth.

Materials and Methods

- PK/PD analysis: HEK 293 cells expressing a doxycycline-inducible cFMS construct were infected subsequently into female NCr nu/nu mice. Tumor bearing animals were randomized into treatment groups and administered 30 mg/kg doxycycline by oral gavage 14 hr prior to ARRY-382 treatment. Mice received a single oral dose of either vehicle or ARRY-382 and sacrificed at the indicated time point. Plasma and tumor drug concentrations were determined by LC-MS, and Western blot analysis was performed to determine phospho-cFMS/total cFMS protein levels.

In vivo LPS challenge: Male Swiss-Webster mice received either a single, oral dose of ARRY-382 or vehicle 30 min prior to an intraperitoneal injection of LPS (3 µg/kg), and animals were euthanized 90 min later. Serum samples were evaluated for TNF-α concentrations by ELISA (R&D Systems) and plasma drug concentrations were determined by LC-MS. Results are expressed as mean ± SEM.

In vivo osteoclast differentiation and bone resorption analysis: Human osteoclast precursor cells (U937) were stimulated with 33 ng/mL M-CSF and 66 ng/mL RANKL for 7 days to induce differentiation of osteoclast lineage precursors to osteoclasts. Cells were fixed and RBCs were lysed (BD Lysing Buffer). Samples were washed and then a set volume was analyzed on a Canto II BD Biosciences flow cytometer. Data were analyzed with FlowJo software (TreeStar). Results are expressed as group mean (red bar) and individual animals (blue diamond). Statistical significance determined by student t-test.

Summary of Results

- ARRY-382 is a highly selective cFMS inhibitor.
- ARRY-382 inhibits human osteoclast differentiation and bone resorption in vitro and blocks TNF-α production in vivo.
- ARRY-382 displays favorable pharmacokinetics in preclinical species.
- ARRY-382 decreases myeloid/macrophage lineages in ID8 tumor ascites.
- ARRY-382 inhibits MCF7-AP1 tumor growth with an accompanying decrease F4/80 (+)-staining cells.

All animal studies were performed in accordance to IACUC guidelines and in harmony with the Guide for Laboratory Animal Care and Use.