Ifetroban for Chemoprevention of Colorectal Cancer in the Pirc Rat

Katie Molind, James Amos-Landgraf

College of Veterinary Medicine, University of Missouri, Columbia, MO (Molind)
Department of Pathobiology, University of Missouri, Columbia, MO (Amos-Landgraf)

Background and Significance

• Familial adenomatous polyposis (FAP) results from a germline mutation in the adenomatous polyposis coli gene, Apc.
• Individuals with this mutation will develop a large tumor burden by their teens or early twenties.
• Current prevention strategies involve surgical intervention coupled with NSAIDs.
• NSAIDs are not completely effective for this purpose and their use is often limited by toxic gastrointestinal and cardiovascular effects.

• Thromboxane (TXA2), a prostaglandin, has been associated with the development of several cancers, including colon cancer.
• TXA2 is thought to play a role in cancer development through increased thromboxane prostanoi receptor (TPr) signaling (Figure 2).
• In malignant tissues TXA2 expression is increased.
• Ifetroban works as a competitive receptor antagonist to prevent TPr signaling (Figure 3).

Methods

Figure 1: Intestinal polyps in a human patient.

• Polyposis in Rat Colon (Pirc) rats will be used as the model in this study due their development of a phenotype like that seen in humans (Figure 4).
• Rats will be assigned to negative control, positive control, and Ifetroban groups.
• Colonoscopies will be performed at 1.5, 2.5, and 3.5 months (Figure 5).
• Necropsies will be performed at 4 months.
• GI tract will be examined to determine tumor burden.
• Other tissues, including the lung, liver, kidney, and heart will be collected to determine if there is major organ tissue toxicity.

Expected Results

• Ifetroban will be at least as effective as Sulindac at preventing polyp formation.
• Ifetroban will have a reduced tumor burden when compared to the negative control.
• Ifetroban will have less major organ tissue toxicity than Sulindac.

Figure 8: Summary of expected results.

References