Ifetroban for Chemoprevention of Colorectal Cancer in the Pirc Rat

Veterinary Research Scholars Program
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Background and Significance

- Familial adenomatous polyposis (FAP) results from a germline mutation in the adenomatous polyposis coli gene, Apc.[1]
- Individuals with this mutation will develop a large tumor burden by their teens or early twenties.[1]
- Current prevention strategies involve surgical intervention coupled with NSAIDs.[2]
- NSAIDs are not completely effective for this purpose and their use is often limited by toxic gastrointestinal and cardiovascular effects.[2]

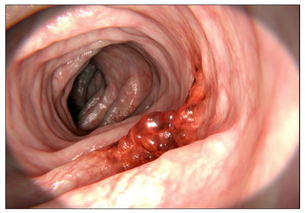

Figure 1: Intestinal polyps in a human patient.[3]

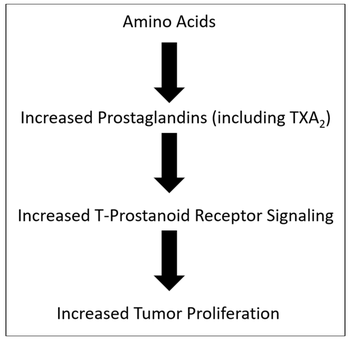

Figure 2: Possible pathway by which COX signaling is correlated to colon cancer.

- Thromboxane (TXA_2), a prostaglandin, has been associated with the development of several cancers, including colon cancer.[4]
- TXA_2 is thought to play a role in cancer development through increased thromboxane prostanoid receptor (TPr) signaling (Figure 2).[4]
- In malignant tissues TXA_2 expression is increased.[4]
- Ifetroban works as a competitive receptor antagonist to prevent TPr signaling (Figure 3).[5]

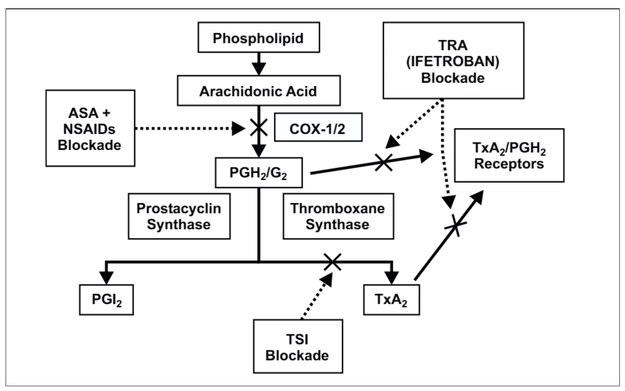

Figure 3: Synthesis pathway for thromboxane and sites of action for aspirin (ASA), NSAIDs, and Ifetroban.[5]

Methods

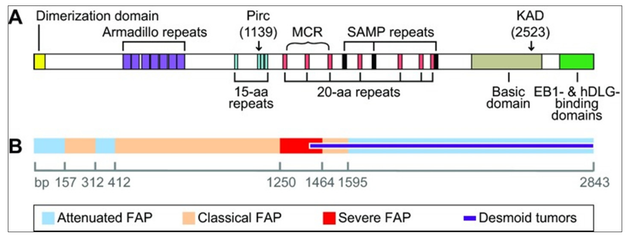

Figure 4: A: Structure of the human APC gene with orthologous Pirc mutation shown. B: Locations of mutations and their correlated level of severity.[1]

- 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).[1]
- 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.

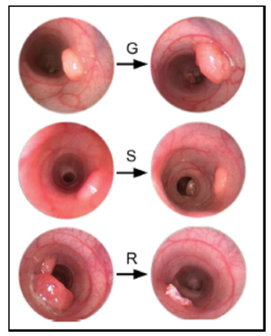

Figure 5: Intestinal polyps visualized during colonoscopy in Pirc rats. Polyps shown here are growing (G), static (S), or regressing (R).[1]

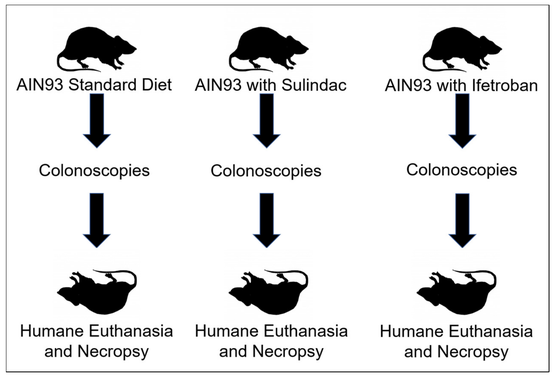

Figure 6: Summary of methods.

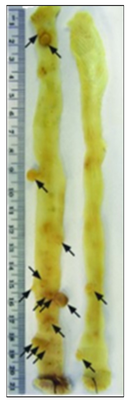

Figure 7: Tumors found in the Pirc rat.[1]

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.

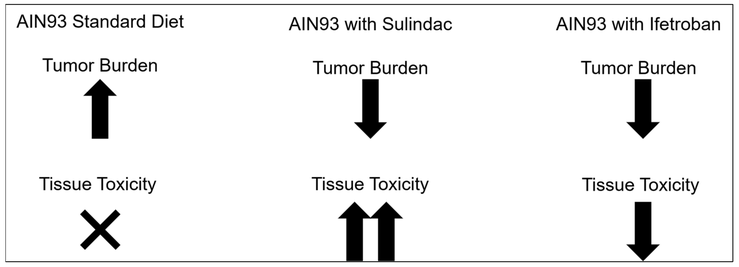

Figure 8: Summary of expected results.

Acknowledgements

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References

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