Macrolid Induced Correction of Premature Stop Codons: A novel Treatment for Colorectal Cancer (Ramot)

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Restoration of premature termination codons (PTCs) caused by nonsense mutations for the treatment of Familial Adenomatous Polyposis.

The Need

Familial Adenomatous Polyposis (FAP) is a high penetrance devastating syndrome manifested by dozens to thousands of colonic adenomas. FAP patients require tight supervision and eventually undergo surgery, to prevent inevitable development of colorectal cancer (CRC) by the third to fifth decade of life. Most FAP cases are attributed to inherited mutations in the adenomatous polyposis coli (APC) gene which is mutated in the majority of both hereditary and sporadic CRCs, and occur very early in the adenoma to carcinoma path, suggesting that APC has a “gatekeeper” function for disease development. Multiple chemoprevention trials have been performed to postpone or prevent surgery in FAP patients, however none are currently routinely employed in the clinical as they were shown to be ineffective or to have strong side effects.
FAP has a birth incidence of about 1/8,300, manifests equally in both sexes. In the EU, prevalence is estimated at 1/11,300-1/37,600 whereas in US is 1/5000-10,000.

Potential Application

Restoring APC expression via read-through treatment may result in adenoma growth stabilization or even regression, and potentially assist in postponing or even preventing surgery all together in attenuated FAP patients that present low/moderate polyp burden. Our strategy suggests:
1. Potential chemo-preventive solution for cancer
2. Personalized approach to therapy according to the type of germline mutation
3. Repurposing of common antibiotics/drugs
4. Prevention or delay of the inevitable surgery in polyposis patients.

Stage of Development

We have recently shown that members of the macrolide antibiotic family, such as Azithromycin and Erythromycin, can induce read-through of the APC nonsense mutations, resulting in reduced oncogenic phenotypes. We have designed a cohort trial to determine the effectiveness of Erythromycin-induced readthrough therapy in FAP patient and investigate the molecular and genetic events underlying adenoma progression.
10 PTC-mediated FAP patients were treated with Erythromycin for 4 months. General polyp burden was monitored following treatment with encouraging results. Seven of the ten patients responded to the treatment according to the posttreatment colonoscopy (at 4 months) and exhibited a reduction in the number and cumulative size of adenomas. A reduction at follow up endoscopy (12 months) was observed in six patients, four of whom were initial responders. Additionally, there was 1 Patient who was not an initial responder per se (the change was in adenoma number) but did show a reduction in adenoma burden at follow-up (12 months) and reduced polyp number after 24 months. Adenoma assessment of the entire study cohort revealed a total decrease in the median of all parameters as compared to baseline measurements and the effect was maintained at 12 months posttreatment. Improvement was observed in molecular and genetic measurements (ki67, APC mutation analysis, active β-catenin expression, APC NGS, C-MYC, AXIN2 and CYCLIN D1) as well.
All in all, our results suggesting that read-through therapy is indeed a potential chemo-preventive approach that may benefit FAP patients.

We aim to further validate Erythromycin effect on FAP adenomas with a randomized, single-blind, cross over study with Erythromycin to Expand and optimize the Erythromycin treatment protocol as

a read-through therapy for polyposis patients that harbor disease causing nonsense APC mutations.

Patents
US 9,486,467 (extended by 1196 days) granted
WO 2007/144876, granted in Europe

Supporting Publications
Kariv R, Caspi M, Fliss-Isakov N, Shorer Y, Shor Y, Rosner G, Brazowski E, Beer G, Cohen S, Rosin-Arbesfeld R. Resorting the function of the colorectal cancer (CRC) gate keeper adenomatous Polyposis Coli (APC). Int J Cancer. 2019 Jul 8

Watch the story on KAN 11 channel: https://www.youtube.com/watch?v=QXzaC-pVl8s

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