Editorial Commentary

The enduring promise of phosphodiesterase 5 inhibitors for colon cancer prevention

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The basis for colorectal cancer (CRC) chemoprevention by cyclic guanosine monophosphate (cGMP)

Cancers of the colon and rectum (CRC) are some of the most commonly diagnosed and are responsible for 9% of all cancer deaths due to the late stage of diagnosis where treatments are largely ineffective. Prevention of CRC is therefore very important for high-risk patients. The average lifetime risk of developing CRC varies widely between countries, but once diagnosed, the risk increases 3–5 folds for first-person relatives and for recurrence in the patient (1). Typical recommendations for the many millions of people in this high-risk category include lifestyle modifications that are typically not specific for CRC, or that have a marginal effect. The most effective measure for CRC prevention is colonoscopy, which can both detect and remove precancerous polyps. While colonoscopy screening has reduced relative risk, up to 25% of polyps remain undetected, and there are many cultural, geographic and economic barriers that limit the availability of this invasive and expensive procedure (2-4). Chemoprevention is therefore very important for CRC, but apart from non-streroidal anti-inflammatory drugs (NSAIDs) that have significant side effects (5), there are currently no drugs approved for this purpose.

A large body of evidence fuels a growing excitement over the potential of cGMP-elevating agents to prevent colon cancer. Uroguanylin and guanylin are peptide hormones that trigger intracellular cGMP production by activating epithelial guanylyl cyclase C receptors (GC-C) (6). GC-C knockout mice are deficient in cGMP and exhibit increased tumorigenesis in both AOM and *Apc*$^{Min/+}$ mouse models of colon cancer (7,8). Moreover, increasing cGMP in wild type mice using exogenous GC-C agonists can suppress tumorigenesis in *Apc*$^{Min/+}$ mice (9-11). Phosphodiesterase 5 (PDE5) is expressed in the intestinal epithelium, and antagonizes the effects of GC-C agonists by degrading cGMP (12). PDE5 inhibitors (PDE5i) amplify the effect of endogenous GC-C agonists, and have recently been shown to block tumorigenesis by 50% in both AOM/DSS and *Apc*$^{Min/+}$ mouse models of CRC (11,13).

The mechanism of CRC inhibition by cGMP

The mechanism underlying the inhibition of CRC by cGMP is still under investigation, but two different ideas have been proposed. The first proposal comes from a large body of work using colon cancer cell lines, and favors the idea that PDE5i can suppress cancer cell proliferation and promote apoptosis. However, most of these are *in vitro* studies that used inhibitor concentrations that are unachievable in humans, and therefore may be clinically irrelevant. Studies *in vivo* using knockout mice with defective cGMP signaling have shown that cGMP controls intestinal homeostasis by slowing epithelial turnover (7,14,15). In addition, oral administration of PDE5i's to

mice causes a reduction in the proliferative compartment in the colon. This is where neoplastic transformation occurs because of replication errors and susceptibility to genotoxic stress. The second proposal is that increased cGMP alters the normal epithelium to make tumor initiation less likely rather than suppress the growth of initiated tumors. Preclinical studies add credibility to this idea because polyp multiplicity was reduced by PDEi, but the size of the initiated polyps was unaffected (11,13). Moreover, sildenafil reduced polyp formation in the AOM/DSS mouse model only when applied during tumor initiation, but had no effect on tumor promotion. Notably, the inhibition of CRC in mice by sildenafil used a clinically relevant dose (5.7 mg/kg per day) that was based upon the amount required to affect intestinal homeostasis (16). While the more detailed cGMP-dependent signaling mechanism remains to be determined, it is important to underscore the notion that cGMP-elevating agents are more likely to be useful for CRC chemoprevention, and are not indicated for treating cancer patients.

A retrospective clinical study in humans

The abundance of preclinical data strongly supports the utility of PDE5i for CRC chemoprevention, but it is unknown whether these drugs will behave similarly in humans. A single clinical study tested the ability of linaclotide to affect cGMP levels in the colorectum of a small number of patients (17) . In patients who responded to the drug (with diarrhea), there was a significant reduction in proliferation (Ki67) in the crypts. This result indicates that the homeostasis effects of cGMP are conserved between rodents and humans, and suggests that the chemoprevention effects might also work in humans.

The most compelling evidence that PDE5 inhibitors might prevent colon cancer in humans came from a recent retrospective study using the Swedish Hospital Discharge Register (1,250,596 person-years of follow-up) (18). The authors queried the database by identifying patients having been “exposed” to PDE5i as those having more than one prescription on record, and those with no prescriptions as “never exposed”. In the overall population they found a hazard ratio of 0.81 for CRC development in those exposed vs never exposed. More importantly, when they looked at a higher risk population with prior polypectomy (4,849 exposed to PDE5i vs 31,171 never exposed), they observed a hazard ratio of 0.64. This 36% reduction in CRC risk is strong evidence to support the potential utility of PDE5i for preventing CRC in high-risk patients. However, there are important caveats regarding the interpretation of retrospective epidemiological studies before determining causation. For example, a provocative study surfaced in recent years that associated sildenafil use with increased risk of developing melanoma (19). However, subsequent studies found a lack of causality because the effect was neither dose-dependent nor specific for melanoma, and was likely due to more frequent healthcare visits among PDE5i users (20,21). The study by Huang and colleagues did find a dose-dependent reduction in risk, with higher dose prescriptions achieving a hazard ratio of 0.6 for those exposed to PDE5i compared to those never exposed. While this lends credibility to causality, other lifestyle issues not addressed by the study could confound conclusions.

A future prospective clinical study

Taken together, the preclinical and epidemiological evidence provide strong rationale for a prospective clinical study to test the efficacy of cGMP-elevating agents on CRC prevention. PDE5i and GC-C agonists had equal efficacy in mouse models of CRC, but the lack of information about long-term use, diarrhea as a common side effect, and a large percentage of patients that are refractory, are obstacles to using GC-C agonists (22). In contrast, PDE5i’s have been used for decades to treat erectile dysfunction patients (since 1998), and have been used chronically to treat pulmonary arterial hypertension (since 2005) and benign prostate hyperplasia (since 2011). This clinical history has demonstrated that PDE5i’s are well tolerated and safe for long-term use. However, they have dose-dependent side effects that patients accept in order to reduce their disease-specific symptoms. Using PDE5i for colon cancer prevention in otherwise healthy people may therefore require dosing to minimize side effects that could otherwise affect compliance.

Another important consideration in a prospective clinical trial for PDE5i’s is which patients to include. The realistic goal of chemoprevention is to reduce the risk of CRC for people who are predisposed, to that of the general population. The highest risk is associated with heritable genetic disorders such as Lynch syndrome and familial adenomatous polyposis (FAP), followed by those with long-standing inflammatory bowel disease (IBD). Almost decades ago, preclinical work with a weak PDE5i called Exisulind prompted clinical trials in FAP patients. Despite some efficacy, it was ultimately not approved due

to hepatotoxicity at therapeutic doses (23-25). Enrolling FAP patients can facilitate statistical powering, but as a relatively rare disease, and with early colectomy as the standard of care; it is unlikely that these patients will be the main beneficiaries of chemoprevention. Similarly, the main concern of IBD patient's is amelioration of their symptoms, and CRC prevention is a secondary issue. An appropriate population for a PDE5i-based CRC chemoprevention strategy are people at higher risk due to familial predisposition, and those with recurrent polypectomy. While much larger numbers are necessary due to the lower incidence of carcinoma in this cohort, they are the most appropriate as the ultimate beneficiaries. In the absence of alternative agents for CRC chemoprevention, and the long safety history of PDE5i's, it is hopeful that any success in a prospective clinical study will lead to a rapid transition to clinical practice.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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