CCR1 inhibitor blocks ex vivo ovulation as a non-hormonal contraceptive candidate

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The prevalent use of hormonal contraceptives, which rely on synthetic progestin to inhibit ovarian follicle maturation and ovulation, is associated with serious side effects such as hormone-related cancers, stroke, depression, and obesity. These complications often result in discontinuation, highlighting the urgent need for innovative non-hormonal contraceptive methods. Therefore, we utilize a 3D hydrogel encapsulated in vitro follicle growth (eIVFG) system that accurately mimics key ovarian functions including follicle maturation, ovulation, and hormone secretion to identify compounds that can block follicle rupture without interfering with ovarian hormone secretion. A total of 1340 compounds were initially screened, resulting in 27 promising candidates that were advanced for in-depth drug development activities, including dose-response testing, structure-activity relationship studies, target identification, genetic validation, and in vivo validation. In this study, we focused on the compound, BX-471, a CCR1 (C-C chemokine receptor type1) specific antagonist, which inhibits follicle rupture dose-dependently without affecting progesterone levels. RNA isolation and quantitative PCR analysis on single follicle were performed to elucidate the molecular pathways influenced by CCR1 inhibition. Our findings suggest that CCR1 is a viable target for the development of a nonhormonal contraceptive method, providing a foundation for further studies. This study represents a significant advancement in the development of non-hormonal contraceptives by establishing a comprehensive ex vivo ovulation screening platform capable of systematically identifying and validating new contraceptive candidates. Supported by: Bill & Melinda Gates Foundation, NIH/NIEHS R01 ES032144 and the ASPET SURF program.