Naked Mole-Rat as Model of Reproductive Aging: In Vitro Germ Cell Expansion and Oocyte IIVM Using the Same Ovary

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Female reproductive aging is characterized by a loss of follicles, the functional units of the ovary, consisting of oocytes surrounded by companion granulosa cells. The quality of the oocytes remaining in the ovary also deteriorates with age. Reproductive aging is associated with adverse reproductive outcomes, including infertility, miscarriages, and birth defects, with such consequences becoming more frequent as women, globally, are delaying childbearing. The adult human ovary is devoid of definitive germline stem cells. As such, female reproductive senescence largely results from the depletion of a finite ovarian follicle pool that is produced during embryonic development. Because the ovarian reserve, which dictates reproductive lifespan, is established in utero, the reproductive aging timeline, in effect, is slated before birth.Research groups around the world have explored different models to study mammalian ovarian development and aging. However, these models only allow us to study specific times in development, and, up to now, it has been impossible to evaluate in the same ovary both the early stages of development and aging. Nevertheless, to each rule, there is an exception. The naked mole-rat (Heterocephalus glaber; NMR) is the longest-lived rodent, with a maximum lifespan of >37 years. Female NMRs

show no decline in fertility or fecundity during their entire lifespan, meaning that the dominant breeding females (also known as “Queens”) will breed until they die. Herein, we characterize how in the naked mole-rat ovary it is possible to study the ovarian reserve, mitotic expansion of the germ cell postnatally and, oocyte in vitro maturationusing the same ovary. Our results confirm that it is possible to induce oocyte in vitro maturation in the naked mole-rat, but also that spindle morphology and the timeline required for maturation is closer to humans than mice.