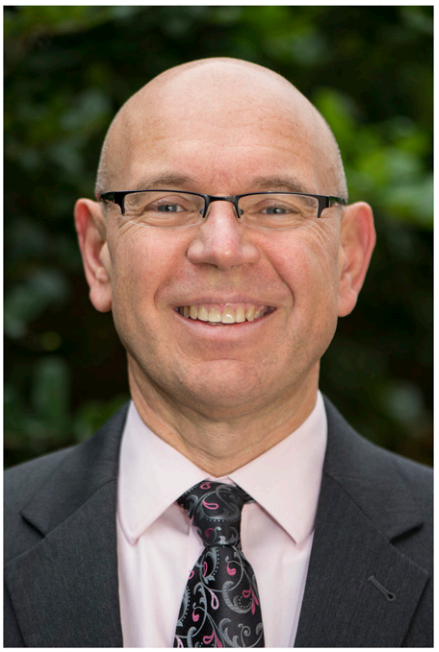
Profile of Martin Matzuk

Jennifer Viegas, *Science Writer*

Martin Matzuk, director of the Center for Drug Discovery at Baylor College of Medicine, recalls a childhood visit to the New Jersey office of orthopedic surgeon Joseph Lepree. "I was always impressed at how full his waiting room was and the time that he spent examining me and speaking with my father," says Matzuk. "On one visit, he asked me what I wanted to be when I grew up, and I said, 'a doctor, just like you.' From that point on, I knew I was going to be a physician." Today, Matzuk is a clinical pathologist and endowed chair in Baylor's department of pathology and immunology.

For nearly three decades, Matzuk's research has focused on the critical proteins and mechanisms involved in reproductive development, leading to advancements in the treatment of infertility and reproductive cancers, such as ovarian cancer. Matzuk and his team have also begun to characterize small-molecule contraceptives targeting the male germ line, paving the way toward the creation of the first effective and nonhormonal birth control pill for men. In recognition of these and other achievements, Matzuk was elected to the National Academy of Sciences in 2014.



Martin Matzuk. Image courtesy of Lynn Zechiedrich (Baylor College of Medicine, Houston).

Introduction to Drug Development

Matzuk's father, Alexander, was a senior research fellow for Merck and Company's research development division in Rahway, New Jersey. He helped develop many drugs, including the fungicide and parasiticide thiabendazole and the antiinflammatory drug indomethacin, which remain on the market today. Matzuk recalls a visit to his father's chemistry laboratory when he was five years old: "I remember being amazed by the stirring bar as it rotated on top of the magnetic stirrer."

His fascination with science extended into his college years as a biology student at the University of Chicago. There, Matzuk met now-deceased biochemist Nicholas Cozzarelli, former editor-in-chief of PNAS. After completing his honor's thesis with Cozzarelli and graduating in 1982, Matzuk moved with the Cozzarelli laboratory to the University of California, Berkeley, where he worked for a year as a staff research associate.

Matzuk then traveled to Washington University, where he earned an MD/PhD in 1989. His graduate advisor was biologist Irving Boime. "Fortunate for me," Matzuk says, "Irv's mentorship still continues, and we talk often and see each other at least yearly." Geneticist Allan Bradley and pathologist Michael Lieberman recruited Matzuk to Baylor College of Medicine in 1991, where he completed his postdoctoral training in mouse genetics and clinical pathology and has stayed for the past 25 years.

Roles of Key Signaling Proteins

During his postdoctoral fellowship, Matzuk conducted research with Bradley and colleagues on the secreted protein inhibin, a member of the TGF-β superfamily. Using mouse embryonic stem cell technology, which was still in its infancy, Matzuk and his team demonstrated that inhibin was a gonadal tumor suppressor (1). The discovery marked the first known secreted tumor suppressor protein.

In three back-to-back papers in 1995 in *Nature* (2–4), Matzuk, Bradley, and colleagues elucidated the roles of activins, which are also TGF-β family members. Countering prior speculation about activin functions, the researchers showed that activins do not signal through activin receptors during mesoderm development, and that the activin-binding protein follistatin does not function in mammalian neural development. Instead, they determined that activin ligands affect craniofacial development of the embryo, and that activin receptor type 2 is the sole activin receptor for the regulation of pituitary follicle-stimulating hormone. When the researchers produced follistatin knockout mice, the rodents died as a consequence of defective skeletal muscle, foretelling future studies of a role of follistatin in antagonizing the signaling of myostatin, a TGF-β family protein that inhibits muscle growth.

A year later, when Matzuk was an associate professor at Baylor, he and his colleagues demonstrated that the oocyte-secreted protein growth/differentiation factor 9

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 7704.

www.pnas.org/cgi/doi/10.1073/pnas.1608856113

(GDF9) could regulate somatic cell function (5). "Before this publication, mammalian oocytes were thought to be merely passengers rather than drivers of ovarian development and early embryogenesis," Matzuk says. "In this paper, we showed that GDF9 is required for ovarian follicles to progress beyond the one-layer ovarian follicle stage. This publication is the first and only description of a knockout mouse model to have this phenotype."

These papers on GDF9, activins, and inhibins marked Matzuk's early investigation of the TGF-β signaling pathway that is involved in many cellular processes affecting both the embryonic and adult stages of an organism. Matzuk and his colleagues have since published more than 160 papers concerning the TGF-β superfamily of proteins, describing their roles in development, reproduction, and physiology.

Genes in Infertility and Contraception

Matzuk's group has determined the function of genes with specific expression in the postnatal male and female germ lines. These genes include *NOBOX*, an oocyte gene required for the initial development of ovarian follicles (6); *TEX14*, a testis-expressed gene essential for intercellular bridges that connect male germ cells during spermatogenesis (7); the structural protein GASZ that is required for small RNA (piwi-interacting RNA) synthesis and male infertility (8); and many others.

Collaborating with cancer biologist James Bradner and structural biologist Stefan Knapp, Matzuk identified a compound, JQ1, that binds with the testis-specific bromodomain protein BRDT that is essential for fertility (9). The researchers showed that JQ1 reduces sperm counts and motility to induce an infertile state in male mice without altering hormone levels or mating behavior. Matzuk says, "This is a good reason to get excited about low sperm counts." When male mice stopped taking the compound, their sperm counts and motility recovered, allowing them to sire healthy offspring. He explained that JQ1-like analogs in the future could lead to the first effective and nonhormonal birth control pill for men.

For Matzuk's Inaugural Article, his team and that of Masahito Ikawa at Osaka University determined that 54 of the more than 1,000 testis-enriched genes in the mouse genome are not essential individually for male mouse fertility (10). The researchers made this determination using Knockout Mouse Project (KOMP) resources and gene editing techniques. Because CRISPR/Cas9 has made it faster and easier to produce knockout mice, Matzuk, Ikawa, and their teams suggest that determining whether or not a gene is essential for male fertility should be tested first in a living organism before significant effort is spent to analyze a gene's molecular function in vitro.

Building a Center for Drug Discovery

Matzuk, a recipient of awards from the Endocrine Society, Pfizer, and the National Institutes of Health among others, received the 2015 Society for the Study of Reproduction Trainee Mentoring Award in recognition of the professional guidance he has given to his over 50 PhD students, postdoctoral fellows, and medical fellows. His leadership skills are now also being applied to his role as director of the Baylor College of Medicine's Center for Drug Discovery.

Since accepting the position in 2012, he has forged a team at the center that collaborates with over 100 principal investigators. The team, which has more than 25 faculty and staff members, continues to grow. Matzuk says, "The vision of the center is to bridge the gap between academic research and pharmaceutical discovery and provide researchers with an economically viable entry into early-stage drug discovery, as well as enabling the study and validation of protein targets and disease mechanisms."

1 Matzuk MM, Finegold MJ, Su J-GJ, Hsueh AJW, Bradley A (1992) Alpha-inhibin is a tumour-suppressor gene with gonadal specificity in mice. *Nature* 360(6402):313–319.
2 Matzuk MM, et al. (1995) Functional analysis of activins during mammalian development. *Nature* 374(6520):354–356.
3 Matzuk MM, Kumar TR, Bradley A (1995) Different phenotypes for mice deficient in either activins or activin receptor type II. *Nature* 374(6520):356–360.
4 Matzuk MM, et al. (1995) Multiple defects and perinatal death in mice deficient in follistatin. *Nature* 374(6520):360–363.
5 Dong J, et al. (1996) Growth differentiation factor-9 is required during early ovarian folliculogenesis. *Nature* 383(6600):531–535.
6 Rajkovic A, Pangas SA, Ballow D, Suzumori N, Matzuk MM (2004) NOBOX deficiency disrupts early folliculogenesis and oocyte-specific gene expression. *Science* 305(5687):1157–1159.
7 Greenbaum MP, et al. (2006) TEX14 is essential for intercellular bridges and fertility in male mice. *Proc Natl Acad Sci USA* 103(13):4982–4987.
8 Ma L, et al. (2009) GASZ is essential for male meiosis and suppression of retrotransposon expression in the male germline. *PLoS Genet* 5(9):e1000635.
9 Matzuk MM, et al. (2012) Small-molecule inhibition of BRDT for male contraception. *Cell* 150(4):673–684.
10 Miyata H, et al. (2016) Genome engineering uncovers 54 evolutionary conserved and testis-enriched genes that are not required for male fertility in mice. *Proc Natl Acad Sci USA* 113:7704–7710.