

Woodruff explores the next generation of tissue chip development

By Eddy Ball

According to Teresa Woodruff, Ph.D., *in vitro* predictive toxicology is poised to take the next big step in modeling, from single-dimension to multi-dimension integrated tissue cultures.

“This is a story that’s really emerging,” Woodruff (<http://fsmweb.northwestern.edu/faculty/facultyProfile.cfm?xid=17133>) told her audience, during a Dec. 4 guest lecture at NIEHS. David Balshaw, Ph.D., program administrator and head of the NIEHS Exposure, Response, and Technology Branch, enthusiastically agreed. “This is one of the most exciting projects in my portfolio,” he said.

Woodruff is a distinguished professor of obstetrics and gynecology, director of the Women’s Health Research Institute at Northwestern University, and immediate past president of the Endocrine Society. She is also the lead researcher on an innovative [grant](http://projectreporter.nih.gov/project_info_description.cfm?aid=8768923&icd_e=22718871) (http://projectreporter.nih.gov/project_info_description.cfm?aid=8768923&icd_e=22718871) to develop an *ex vivo* microfluidic reproductive tract model.

This grant is funded by NIEHS, the National Center for Advancing Translational Sciences, the Office of Women’s Health Research, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development — all part of the National Institutes of Health.

Modeling the female reproductive tract and hormonal cycle *in vitro*

As Woodruff explained, her modeling projects are striving to address the issue of extrapolation from cell cultures and other species to humans. Her FemKUBE is a distinct 3-D tissue-engineered model of the female reproductive tract, including the ovarian follicle, fallopian tube, uterus, and cervix. Woodruff’s goal is to physically link them, but currently they are stand-alone models.

While preclinical toxicity testing in animal models is a cornerstone of the drug development process, it can be controversial and expensive, and it is often unable to predict adverse effects and tolerability issues in human subjects. Predictive toxicology is increasingly exploring alternatives, such as *in vitro* high-throughput screening and tissue chip models, to prioritize chemicals and address the massive backlog of untested compounds.

Even though Woodruff is the first to admit there are many challenges ahead, her team has already defied conventional wisdom with the ability of its FemKUBE model to mimic, with unprecedented fidelity, the elegant hormonal orchestration of the dynamic 28-day female menstrual cycle. FemKUBE uses mouse follicle, but the rest of the model — the cervix, vagina, uterus, fallopian tube, and ovary — consists entirely of human tissue.

Woodruff has used FemKUBE to assess the impact of exposures on the female reproductive tract, including known endocrine disruptors and reproductive toxicants, as well as compounds with unknown toxicity, such as the oil dispersant Corexit, which was used following the 2010 Deepwater Horizon oil spill.

Working toward a human on a chip

While Woodruff’s work, to date, has focused on female reproduction, she is looking beyond women with the concept of a comprehensive repro-on-a-chip model. She considers the development of female and male (DudeKUBE) reproductive microfluidic systems as critical to sex-based *in vitro* toxicity and drug testing.



Woodruff is a dynamic speaker who uses movement, gesture, and eye contact to capture the audience’s attention and communicate enthusiasm for her work. (Photo courtesy of Steve McCaw)



Woodruff credited Balshaw, center, with helping sell her proposal to reviewers. Along with his colleagues from the NIEHS Division of Extramural Research and Training, several in-house lead researchers attended the talk, including Carmen Williams, M.D., Ph.D., right, head of the Reproductive Medicine Group. (Photo courtesy of Steve McCaw)



National Toxicology Program scientists were also on hand for the presentation, including postdoctoral fellows Natasha Catlin, Ph.D., left, of the Developmental and Reproductive Toxicology Group, and Georgia Hinkley, Ph.D., of the General Toxicology and Cancer Group. (Photo courtesy of Steve McCaw)

One motivation for starting with the FemKUBE, Woodruff explained, was the critical and underappreciated role of hormone signaling in health and disease throughout the body. With [tissue chip grants](http://www.ncats.nih.gov/research/reengineering/tissue-chip/funding/funding.html) awarded in 2012 and 2014, other tissue culture developers are working on models, such as heart-liver-vascular systems, circulatory system and integrated muscle tissue, neurovascular system, kidney, stem cells, and specific diseases and disease processes.

These models represent an important step toward integration of individual organs and systems into a so-called human-on-a-chip model for mimicking health effects throughout the human body.

Citation: Eddie SL, Kim JJ, Woodruff TK, Burdette JE.

(<http://www.ncbi.nlm.nih.gov/pubmed/24737736>)

2014. Microphysiological modeling of the reproductive tract: a fertile endeavor. *Exp Biol Med* (Maywood) 239(9):1192-1202.

The potential of tissue chip models

Now in development in Woodruff's lab, 3-D microdynamic models of the reproductive system promise to pave the way for important discoveries, such as the following:

- Better understanding sex-based differences in response to drugs and environmental exposures
- Improving fertility treatment, including oncofertility for reproductive issues related to cancer treatment
- Determining response to hormones and endocrine-disrupting chemicals, particularly for vulnerable populations
- Providing a human correlate for drug development, especially for those medications given to pregnant women
- Advancing predictive toxicology and disease prevention

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