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New University Laboratory Bridges Development Path for Promising Drug Compounds

The new Translational Drug Development Core laboratory at the University of Florida provides services and expertise in bioanalysis, drug metabolism, and preclinical pharmacokinetics in order to help faculty and other partners move promising compounds from the lab into preclinical studies

Products: ACQUITY™ UPLC™ I-Class, ACQUITY UPLC I-Class PLUS, Xevo™ TQ-S micro Tandem Quadrupole System, PDA (photodiode array) and ACQUITY QDa™ detectors, Empower™ Chromatography Data System, MassLynx™ Mass Spectrometry Software

DRUG DEVELOPMENT AT THE TRANSLATIONAL DRUG DEVELOPMENT CORE

The Translational Drug Development Core (TDD Core) laboratory at the University of Florida (UF) Clinical and Translational Science Institute was recently developed to help scientists succeed in moving promising drug compounds from the lab into preclinical studies. With the TDD Core's services, researchers can meet the short intellectual property timelines from provisional to full patent to licensing, enhance federal funding, and accelerate the transformation of new therapeutic interventions for the treatment and prevention of diseases.

The TDD Core team provides:

- Consultation regarding testing, collaboration, and licensing submission
- Laboratory services to assist in advancing a lead compound based on *in vitro* data, in order to transition to full-blown preclinical studies
- Bioanalytical services to define the full *in vivo* pharmacokinetic profile (Absorption, Distribution, Metabolism, and Excretion-ADME) of a compound.

The TDD Core is committed to the teaching and training of future drug discovery scientists. Photo credit: Louis Brems, UF Health.

WORKING WITH WATERS

Dr. Christopher R. McCurdy, director of the TDD Core, started working with Waters™ instrumentation during his tenure at the University of Mississippi, where his research areas included the development of drug compounds for the treatment for pain, anxiety, analgesia, mental disorders, and substance use disorders. He describes: "I had an excellent working relationship with the Waters representative at the time. In our experience, Waters has provided outstanding customer service and attentiveness to our research."

When Dr. McCurdy launched the TDD Core laboratory, he relied on Waters to help build a laboratory with the advanced technology needed to perform its mission. He sees further opportunities to collaborate in the future.

"The Waters support staff and the chemistry staff in the field are excellent and very responsive. We've also been working on some creative ideas with Waters to develop educational offerings around drug development. We really want to expand our working relationship in ways that benefit both of us."

With its 2112 ft² facility in the university's Stetson Medical Science Building, the TDD Core laboratory is fully equipped for pharmacokinetic studies, metabolism studies, permeability studies, analytical method development, dissolution studies, and stability studies. Three full-time researchers, one research coordinator, three graduate students, and one part-time technician help university partners with a clear, precise plan to moving a drug compound forward.

"The objective of the TDD Core facility is to build intellectual property (IP) from research at the University of Florida and develop it in-house. For example, our team can help clients take preclinical candidates that have shown good drug-like prospects, and maybe now need to move into another grant funding phase or towards a further development stage. The goal of TDD Core is to facilitate that process not only more efficiently, but also more cost-effectively than contracting it out to a third party."

DR. CHRISTOPHER R. McCURDY
Director of the TDD Core

With the help of Waters instrumentation and software, the creation of the TDD Core laboratory charts new territory for the university in its internal drug development process. In addition, it provides a resource to the regional universities and biotech start up companies.

FOUNDING OF THE TDD CORE

On April 22 2013, a bill to elevate the national stature of Florida's public universities was signed into law by Gov. Rick Scott. The Florida Preeminence Initiative enabled UF to recruit 100 faculty members with good track records of attracting funding to the university.

Part of the initiative focused specifically on drug discovery and development, which brought a number of new faculty to the six health science colleges of UF Health, and specifically the UF College of Pharmacy.

Two of those new faculty members were Dr. McCurdy and his research partner and spouse, Dr. Bonnie Avery, who were tasked with building a new drug development core facility from the ground up.

Dr. McCurdy explains: "The original vision was to help researchers at the university take their discoveries from the laboratory and move them towards clinical research. What we did was essentially take the paradigm that Dr. Avery and I had developed together in our own research, and then expand into something that would mimic a contract research and development organization (CRDO). Ultimately, this new facility would provide all of the assays necessary for someone to put an investigational new drug application together internally to submit to the FDA."

That initiative led to the development of the TDD Core laboratory. Dr. McCurdy and Dr. Avery established an expert team to evaluate researchers' needs and provide direction for the next steps in the drug development process. Today the TDD Core's services include:

- Planning any needs for bioanalytical or animal testing
- Direction to appropriate collaborators for measurement of other endpoints where necessary, or to other services/ companies for outsourcing when most appropriate
- Assistance/guidance on preparation of relevant data for licensing submission.

These services help UF faculty bridge the gap between the discovery of a promising compound and the drug development process. As a result, researchers can meet the short intellectual property timelines from provisional to full patent to licensing; enhance federal funding; and accelerate the transformation of new therapeutic interventions for the treatment and prevention of diseases. Dr. McCurdy describes the facility's clientele:

"Our primary mission and our primary target is the University of Florida stakeholders – any faculty members or projects within the university take priority over anything else. Companies that are spin-outs or startups from the University of Florida also get priority. We've had a nice mixture of companies that have been affiliated to the university, but the majority of our clients have been within the university system."

In addition to its research goals, the TDD Core also remains committed to the education of UF students. Dr. McCurdy and his team see a role in the laboratory's teaching and training of future drug discovery scientists, while generating creative breakthroughs that lead to technologies with positive benefit, creating opportunities for economic growth in the state, and changing the trajectory of young people through education.

Dr. McCurdy describes this ambition for the TDD Core: "I think the TDD Core offers a tremendous educational opportunity for the students because they get interdisciplinary training. They have to present their findings to the bigger teams and really learn how to communicate with people from multiple disciplines. We have a vision of becoming a preeminent and initial model in academia too, to really help foster development within the program."

The ability to build the TDD Core from the ground up enabled Dr. McCurdy to acquire advanced instrumentation and software to meet the facility's goals. Photo credit: Louis Brems, UF Health.

WATERS INSTRUMENTATION AND SOFTWARE

The ability to build the TDD Core from the ground up enabled Dr. McCurdy to acquire the most advanced instrumentation and software to meet the facility's expansive goals. His previous experience with Waters led to the acquisition of Waters ACQUITY UPLC I-Class Systems and the Xevo TQ-S micro Tandem Quadrupole Systems, among others. The combination of the Waters ACQUITY UPLC with the Xevo TQ-S micro tandem quadrupole mass spectrometer is particularly useful for the TDD's most demanding quantitative UPLC-MS/MS applications.

Like any drug development laboratory, the TDD Core is constantly looking to increase sample throughput and reduce turnaround times, quantify more analytes per sample, and contend with more complex sample matrices. The Xevo TQ-S micro provides the sensitivity and robustness required by the university's drug development services, including qualitative information and accelerated method development.

"The Xevo TQ-S micros are running essentially 24/7, and the only downtime is when we switch projects. We've really been able to expand the capabilities by adding on sample manager systems, so we can robotically run those instruments unmanned for 48 to 72 hours. We run them over the weekend or overnight, and because of that capability, we're able to do a lot of work."

DR. CHRISTOPHER R. McCURDY
Director of the TDD Core

DR. BONNIE AVERY: A UNIQUE LEGACY

Dr. McCurdy founded the TDD Core with his research partner and spouse, Dr. Bonnie Avery, who passed away in 2019.

Dr. Avery brought her unique expertise to the project, including research in analytical chemistry, pharmacokinetics, and drug metabolism of novel, potential drug candidates, as well as complex natural product mixtures.

Her most recent work with *Mitragyna speciosa* afforded her with large grant funding from the National Institute on Drug Abuse (NIDA) and an appearance in the recent documentary "A Leaf of Faith."

Dr. Avery and Dr. McCurdy both called the creation of the UF TDD Core "the career opportunity of a lifetime."

Dr. McCurdy explains: "We started with Dr. Avery's and my analytical expertise and drug development expertise. Since then, we've really progressed with that vision of becoming a fully functional contract research organization within the university. And I don't think that exists, as far as I know, anywhere else in the world."

NATURAL PRODUCTS RESEARCH

The TDD Core laboratory is also heavily involved in natural products research, a speciality of UF. The university describes its drug discovery and development research as natural products-centric, particularly the identification of unexplored organisms. The TDD Core's expertise in analyzing complex natural products, coupled with the advanced instrumentation and software from Waters, enables the team to simultaneously quantify multiple molecules from plant material, as well as translate that research into a clinical trial environment.

Dr. McCurdy describes the TDD Core's role in natural products analysis: "We can look at the pharmacokinetics and the exposure of the different compounds in natural products supplements. So, it's not just drug development. We're working to understand what's going on all the way back to the agriculture, the production of compounds in the compound profiles, and in the plants as they're growing in the fields."

For example, corynantheidine, a minor alkaloid found in *Mitragyna speciosa* (Korth.) Havil, has been shown to bind to opioid receptors and act as a functional opioid antagonist, but its unique contribution to the overall properties of kratom remains relatively unexplored. Dr. McCurdy and his team developed and validated a fast, simple, and sensitive UPLC-MS/MS method using Waters instrumentation in accordance with the FDA guidelines for the quantification of corynantheidine with potential actions at opioid and adrenergic receptors.

This study was the first to evaluate preclinical pharmacokinetic studies in plasma, as well as the distribution and accumulation of the compound in the brain. The information obtained from these studies will facilitate the future research into uncovering the properties of corynantheidine and its contribution to the pharmacology of kratom.[1]

"We're evaluating *Mitragyna speciosa* as a replacement or a treatment for opioid use disorders. We're working on moving that into clinical trials to see if we can affect opioid withdrawal syndrome and opioid use disorders with that plant."

DR. CHRISTOPHER R. McCURDY
Director of the TDD Core

Industrial hemp is another natural products research area of particular interest in Florida, as the state explores the economic value of new agricultural crops. The University of Florida Institute of Food and Agricultural Sciences (UF/IFAS) Industrial Hemp Pilot Project aims to support the future viability and sustainability of the hemp industry through assessment of the crop, cropping systems, and their ecological and economic impacts.

The TDD Core laboratory charts new territory for the university in its internal drug development process. Photo credit: Louis Brems, UF Health.

Industrial hemp is a *Cannabis sativa* plant that has been cultivated for 10,000 years as a fiber and grain crop with modern applications for textiles, building materials, seed oil, and essential oil. Legally, the key difference between hemp and marijuana is the presence of tetrahydrocannabinol (THC), the main psychoactive cannabinoid found in cannabis. Hemp must contain 0.3 percent or less of THC content by dry weight.

Dr. McCurdy describes the TDD Core's role in the project: "We're heavily involved in the state of Florida's industrial hemp initiative. We were the analytical laboratory for the state's research into industrial hemp and cannabidiol (CBD) containing cannabis products. In 2018, the Farm Bill mandated the United States Department of Agriculture to develop regulations governing the cultivation, processing, and marketing of industrial hemp. For hemp to become an agricultural commodity, it is important to regulate production by developing standard methods for sampling and testing of the plant material."

Dr. McCurdy and his team developed a UPLC-MS/MS method using Waters instrumentation for the quantification of twelve cannabinoids. The method was applied to a regulatory sampling trial of three hemp varieties cultivated for CBD production. The results indicate that the way hemp is sampled and analyzed may influence the legality of a crop, which could have negative economic and legal consequences.[2]

Dr. McCurdy describes this research: "Industrial hemp is a complex botanical mixture. The ability to simultaneously identify multiple cannabinoids was important because you needed to know what precursors were present to THC production. As a result, you could adequately estimate what the actual THC levels would be, since that's what's really being monitored from a legal standpoint."

BUILDING ON THE SUCCESS SO FAR

Just as COVID-19 hit the United States in early 2020, the TDD Core planned to open its new fully renovated laboratory facility. As a result, the original schedule for expanding the laboratory's services and clientele was delayed.

Dr. McCurdy describes the effect of the university's COVID-19 shutdowns: "The University of Florida and the College of Pharmacy were instrumental in making our renovated space happen. We really put together a state-of-the-art analytical facility. We were in the process of planning a grand-opening, ribbon-cutting ceremony when COVID happened. We were excited to finally unveil ourselves to the world – and then the world stopped."

However, as things have slowly returned to normal, the TDD Core team plans to continue to build on its success in facilitating the research of UF faculty and related partners. That includes increasing effective agreements between researchers and funding opportunities, marketing the laboratory's research capabilities to collaborators and funding agencies, and forging institutional relationships with external stakeholders. Dr. McCurdy sees Waters continuing to have a large role in supporting the development of the facility.

"We have a beautiful relationship with Waters; the team is excellent and very attentive. We receive a lot of support from them, and they always work very quickly to help us resolve any challenges in the lab."

DR. CHRISTOPHER R. McCURDY
Director of the TDD Core

While the TDD Core has already accomplished a great deal for the university, Dr. McCurdy sees multiple opportunities to expand the laboratory's services and clientele.

He explains: "While the TDD Core is primarily set up for researchers within the University of Florida, we've also been working with small biotech companies in the area, just through word of mouth. We've started to get grant contracts with other universities in the Southeast and in the central part of the United States. And we're just getting started. We've been able to get more grants funded. We've been able to contract with more outside partners and and move forward with things so much that we're actually growing in logarithmic units in terms of our financials and customer base. Now that we're fully operational, our capacity is much greater. We can handle more work, and we're getting the word out."

References

1. King et al. Bioanalytical Method Development and Validation of Corynantheidine, a Kratom Alkaloid, Using UPLC-MS/MS, and Its Application to Preclinical Pharmacokinetic Studies. *Journal of Pharmaceutical and Biomedical Analysis*, **2020**, 180, 113019.
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Waters Corporation
34 Maple Street
Milford, MA 01757 U.S.A.
T: 1 508 478 2000
F: 1 508 872 1990
waters.com