COMPUTATIONAL MODELING OF LOCAL DRUG DELIVERY

Combination drug-eluting device designs pose novel challenges in their development and regulatory approval. Appreciation and control of their performance defies intuition and is now too complex for observational studies in animals and humans alone. With the encouragement of the FDA, computational techniques are increasingly used to bridge this gap and to consider the fullest range of possible anatomic-pathologic scenarios, along with material and drug perturbations, to predict events and areas of concern. CBSET is a pioneer and leader in this space, leveraging its expertise in experimental and modeling techniques to study the mechanisms underlying device implantation, elution kinetics, efficacy and safety. Our experienced team of professionals will develop an integrated research program of *in vivo*, benchtop and computer studies to identify the rate-limiting process governing elution from your devices and to predict the spatio-temporal patterns of drug distribution that they achieve in appropriate animal models. Our mechanistic approach provides a powerful paradigm by which to optimize your devices, educate your clinical and regulatory constituencies and streamline the regulatory process.

CBSET—SPECIALIZED EXPERTISE DEVELOPING MODELS FOR *IN VIVO* DRUG RELEASE, TISSUE DISTRIBUTION AND RECEPTOR BINDING

Controlled release and biodegradation: Polymeric controlled-release devices have revolutionized the practice of medicine, offering a means of tailoring and optimizing release kinetics and polymer degradation. Computational modeling offers an efficient framework for developing these technologies and understanding their mode of operation. CBSET is a leader in modeling drug-release kinetics from durable and biodegradable controlled-release particles, matrices and coatings consisting of natural and artificial polymers. CBSET develops computational models that help our partners understand the dependence of *in vitro* and *in vivo* elution kinetics and polymer content on drug solubility, polymer type and molecular weight, drug/polymer ratio and crystallinity, binding interactions, mixing condition, composition of release media and variations of the in-vivo environment.

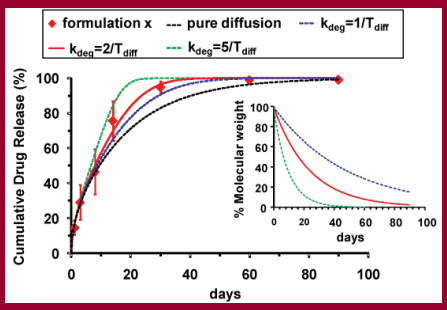
Drug distribution and tissue pharmacology: Efficacy of local drug delivery is often limited by poor distribution due to physiological barriers such as low-permeability tissue layers, clearance by blood, metabolism, non-specific binding and even binding to receptors. CBSET couples cell surface receptor binding and dose-response data, HPLC, histopathology, fluorescent imaging, OCT and computational modeling to quantify drug distribution patterns and their dependence on drug properties, release kinetics, device geometry and orientation, and disease state. CBSET uses this integrated methodology to support research and development goals, regulatory submissions and marketing objectives of endovascular drug-eluting devices, microparticle-based growth factor therapies, and implanted devices in normal and neoplastic tissue.

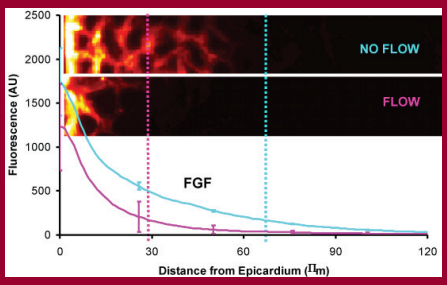
CBSET specializes in computational models that couple tissue pharmacokinetics with receptor pharmacology to provide unique insights into the determinants of local drug effects. Through the development of such mechanistic PK/PD models, CBSET provides partners with unique insights into the dependence of local biological effects on device geometry, drug dose and release kinetics.

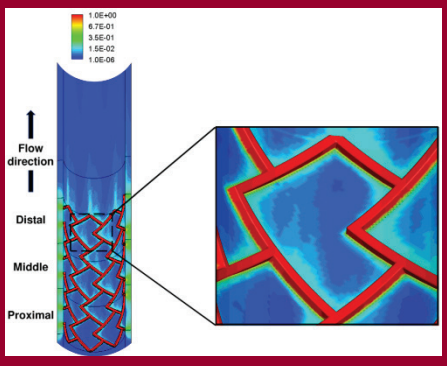
Device-tissue interactions: Device implantation perturbs the biological environment in unforeseen ways. Experimental assays can provide snapshots of the pathological consequences of device presence but lack predictive power. To address this challenge, CBSET builds on its expertise in pathology to develop realistic computational models that predict device-induced pathologies, and the latter's influence on drug distribution. For example, we have used this approach to predict the influence of endovascular device geometry on blood flow, thrombosis, drug absorption and distribution.

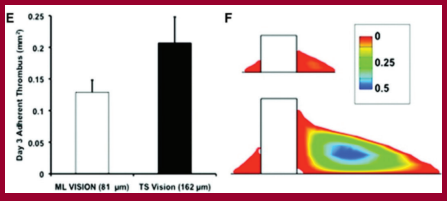
THE CBSET PROCESS

1. Study Design/Development
2. Experimental Execution
3. Histopathology/Pathology
4. Data Analysis & Reporting









ABOUT CBSET

CBSET is an AAALAC accredited, not-for-profit, pre-clinical research organization dedicated to research, education, and the advancement of early-stage biomedical technologies. Our mission is to assist in methodologies uniquely suited for novel and innovative treatments for complex diseases. We offer a full range of GLP and non-GLP services, ranging from early product evaluation through lead optimization and pre-clinical safety, to physician assessment and training courses. We specialize in the development and application of techniques in the fields of cardiology, electrophysiology, orthopedics, wound healing, regenerative medicine, endoscopy/laparoscopy, drug and device delivery and safety, cellular therapy, and diagnostic imaging. Our world-renowned regulatory and scientific expertise helps transform early-stage concepts into novel therapies.

CBSET EXPERTISE

Our professionally trained staff and consultants provide expertise for all phases of biomedical discovery and development research including regulatory consulting, veterinary medicine, surgery and minimally invasive surgery, imaging, pharmacokinetics and drug metabolism, drug and device safety, pharmacology, lead optimization, and specialized histopathology and pathology. These individuals provide the basis for successful scientific collaborations, rapid concept advancements, unparalleled consultation services, and expert dissemination of information and findings to regulatory and scientific bodies.

CBSET offers a full range of GLP and non-GLP services, from early product evaluation through lead optimization and pre-clinical safety, to physician assessment and training courses. Our expertise includes:

- Stents/balloons
- Novel catheters/wires
- Robotic-assisted surgery
- Vessel sealing/closure devices
- Heart valve replacement/repair
- Cardiopulmonary bypass
- Beating heart technology
- Electrophysiology devices
- Tissue ablation devices
- Endoscopic/NOTES surgery
- Laparoscopic surgery
- Orthopedic devices
- Novel surgical instruments
- Wound healing devices
- GLP training and regulatory consulting

CBSET
YOUR TECHNOLOGY, OUR MISSION

CBSET FACILITIES

CBSET offers an unparalleled, GLP-compliant, 30,000 square foot state-of-the-art facility within minutes of Cambridge, Boston, and Logan International Airport. Our facility includes vivariums, catheterization/imaging labs, and full surgical suites containing the latest equipment for fluoroscopy, echocardiography (TEE/TTE), electrophysiology, IVUS, optical coherence tomography (OCT), endoscopy/laparoscopy, orthopedic surgery, and surgical video recording. CBSET offers dedicated labs for GLP-compliant SEM, specialty histopathology/pathology, metabolism and pharmacokinetics

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