# CPRIT-FUNDED CORE NETWORK

Suzanne Tomlinson, PhD MBA

smtomlin@rice.edu

Gulf Coast Consortia

QUANTITATIVE BIOMEDICAL SCIENCES

*Gulfcoastconsortia.org*

# GCC INNOVATIVE DRUG DISCOVERY AND DEVELOPMENT (IDDD)

- Formed in 2003

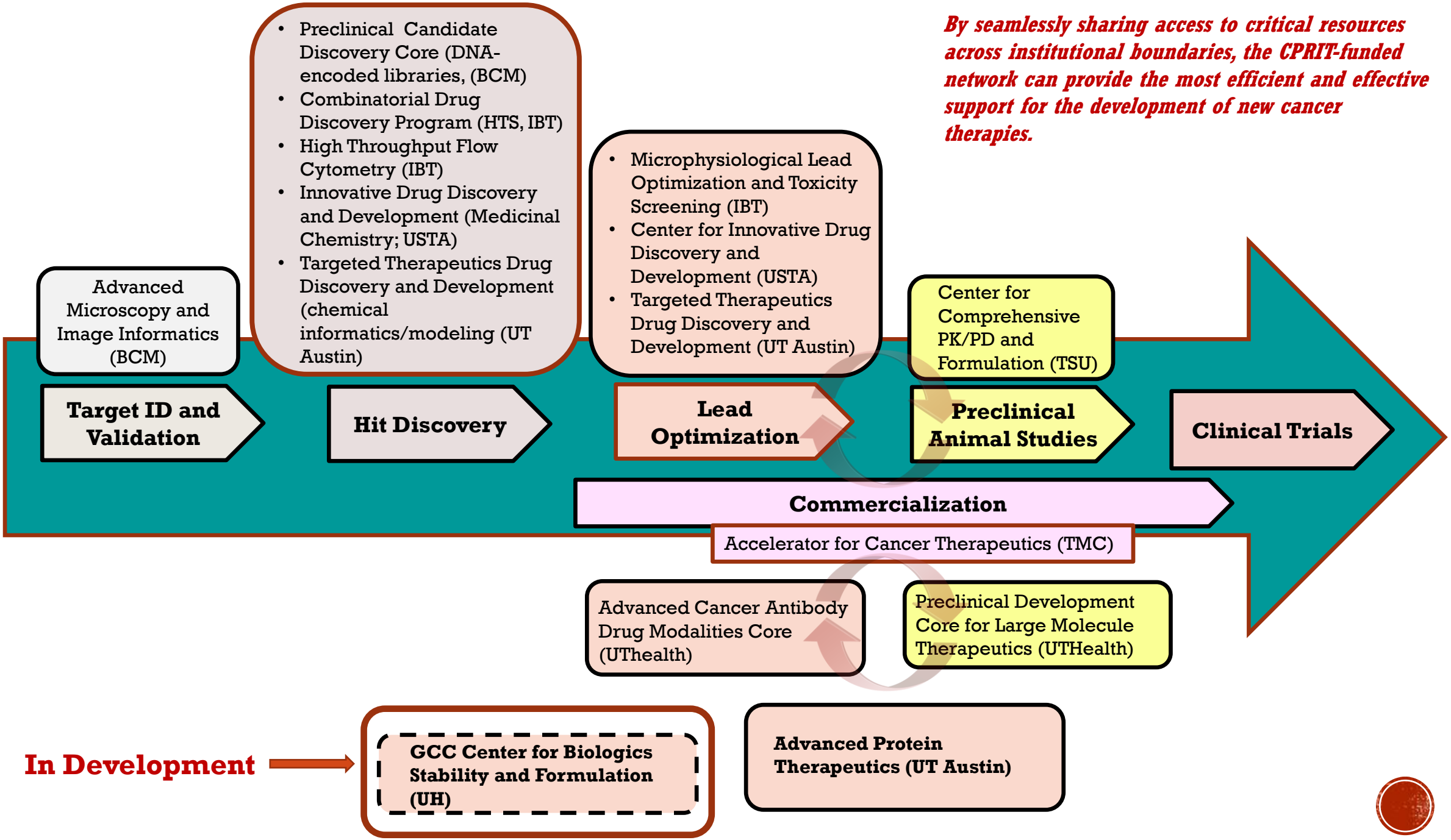
- Focused on providing support for Houston/Galveston (and beyond) scientists in advancing their therapeutics discoveries through development to the clinic.

- IDDD support includes collaborative networking and joint funding opportunities, shared core resources, and educational programs.
  - CPRIT-funded Cancer Therapeutics Training Program
  - Round-Table Workshop Series
  - CPRIT-funded Core Network

Gulf Coast Consortia

QUANTITATIVE BIOMEDICAL SCIENCES

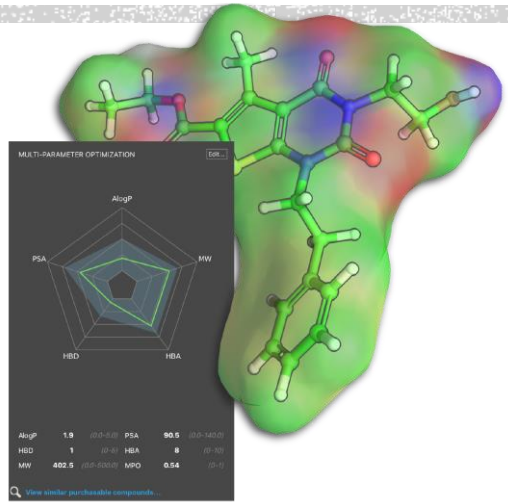
***By seamlessly sharing access to critical resources across institutional boundaries, the CPRIT-funded network can provide the most efficient and effective support for the development of new cancer therapies.***



# ACCELERATOR FOR CANCER THERAPEUTICS

**Director: Tom Luby, TMC Innovation**

**Advanced Computational Lead Optimization**



# ADVANCED PROTEIN THERAPEUTICS (APT) CORE

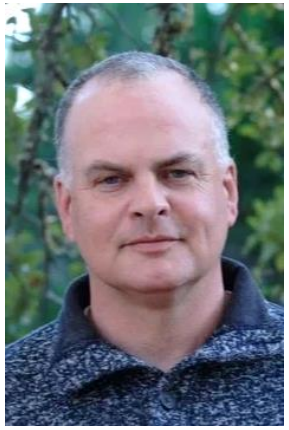
This new CPRIT-funded facility at The University of Texas at Austin will leverage Texas' historic strengths in cancer research by catalyzing translation of scientific discoveries into novel therapies

APT Principal Investigator:
**Jennifer A. Maynard, Ph.D.**
*Professor of Chemical Engineering*

Expertise in developing antibody and T cell receptor-based therapeutics to address unmet medical needs.

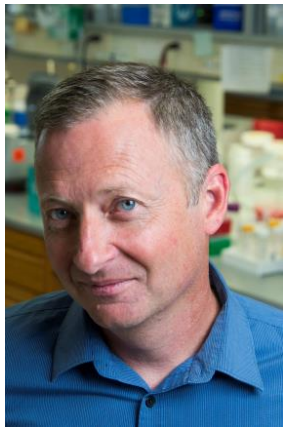
APT Director:
**Annalee W. Nguyen, Ph.D.**
*Research Associate, Chemical Engineering*

20+ years experience in protein engineering and 10+ years experience in laboratory management.



APT Co-Investigator:
**Kevin N. Dalby, Ph.D.**
*Professor in Pharmacy*

Expertise in the medicinal chemistry and the synthesis, purification, and analysis of protein conjugates.



APT Co-Investigator:
**Everett Stone, Ph.D.**
*Professor, Molecular Biosciences*

Expertise in the engineering of human enzymes for cancer therapy.

# APT CORE CAPABILITIES

## Biologics production & characterization

- Antibody IgG production with different isotypes and designer Fc domains to tailor effector functions
- Design and production of various bispecific antibody formats
- Generate protein-drug conjugates
- Enzyme production and activity analyses
- CHO, HEK and bacterial expression capabilities

## Biologics discovery & engineering

- Cloning & humanization of established hybridomas
- Generation of antibody panels from nanomice, humanized mice and human PBMCs
- Engineering via three display platforms (phage, yeast, mammalian)
- Engineering of TCRs and TCR-like antibodies
- Engineer enzymes to reduce immunogenicity, increase activity and selectivity

## Cellular assays & mouse models

- *In vitro* antibody-dependent cellular cytotoxicity and phagocytosis assays
- Pharmacokinetics in FcRn-humanized mice
- Murine tumor models

## Outreach & training

Summer workshops with training modules in:

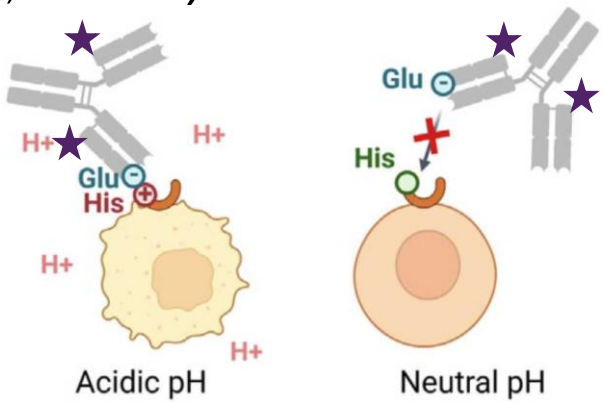
- Antibody discovery
- Phage display for antibody engineering
- Yeast display for antibody engineering
- Mammalian cell display for antibody engineering
- Enzyme activity screens for engineering

# EXAMPLE APT PROJECTS

## pH-selective targeting and killing of tumor cells

*collaboration with the Ueno Lab (Naoto Ueno, M.D., Ph.D.)*

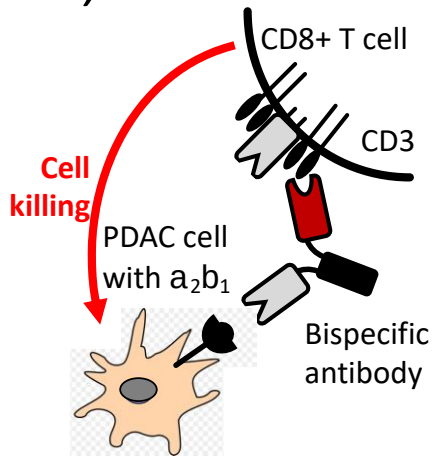
**Selective binding** in the acidic tumor microenvironment with delivery of a toxic payload




## Bispecific targeting of $\alpha_2\beta_1$ integrin on pancreatic cancer stem cells

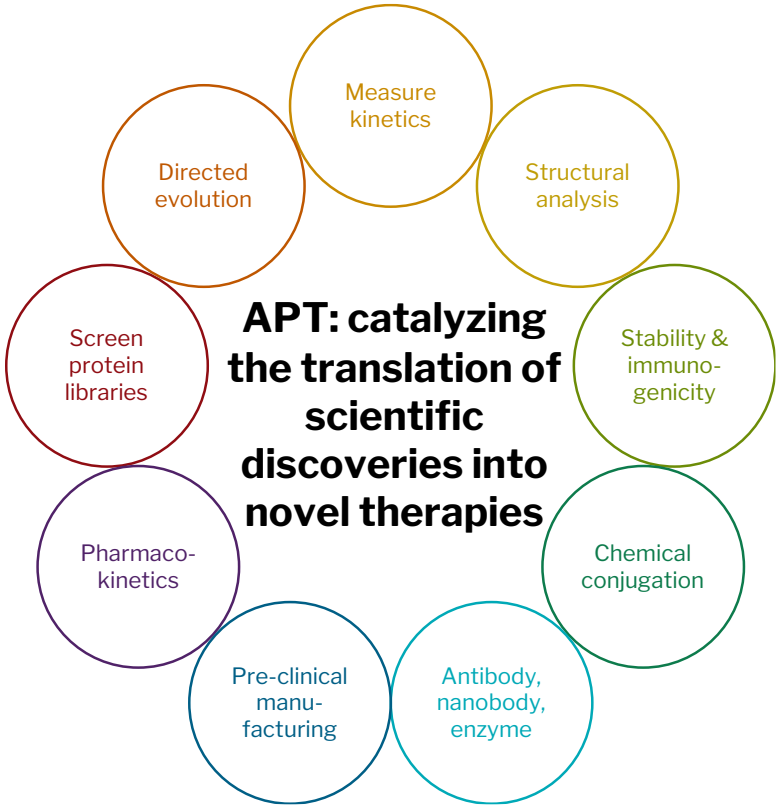
*collaboration with the Matsui Lab (Bill Matsui, M.D., Ph.D.)*

**Redirect polyclonal T cells** to tumor suppression



# APT CORE PARTNERSHIPS

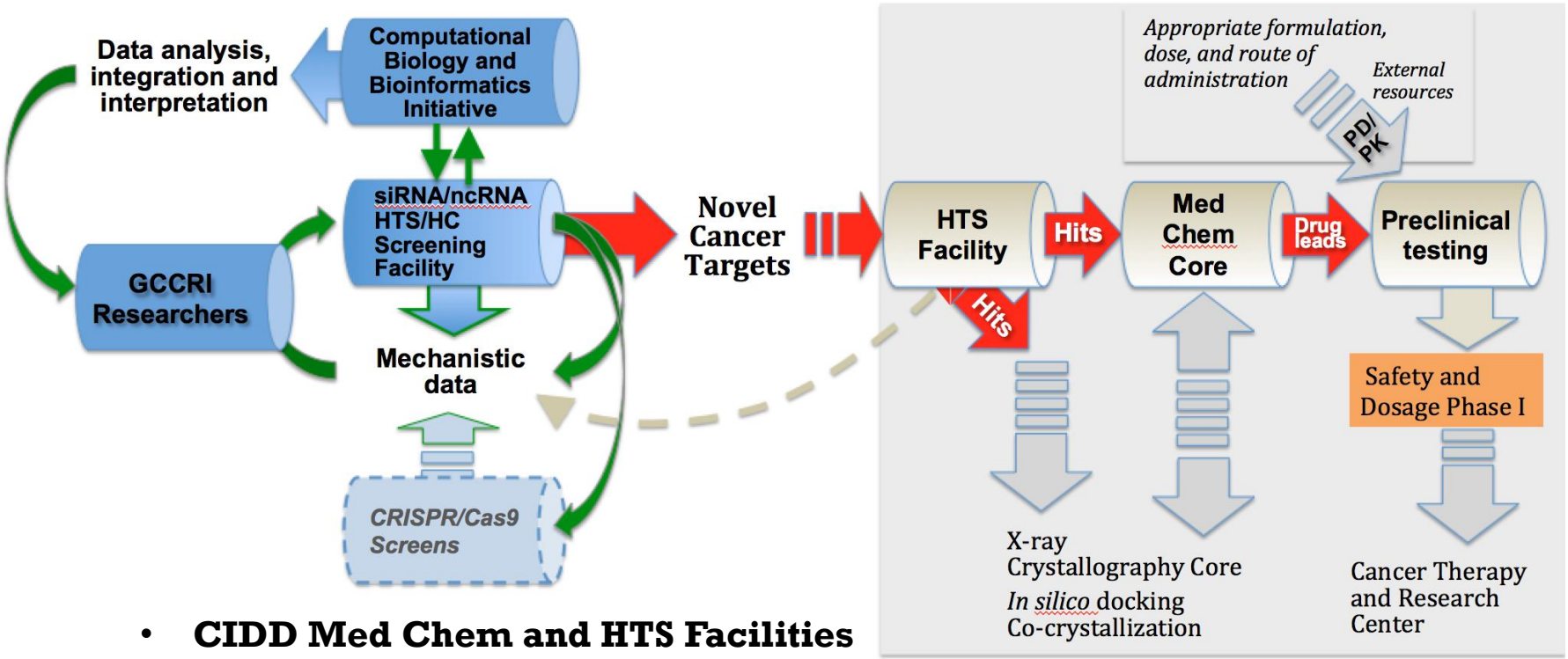
- **G**ulf **C**oast **C**onsortia for Innovative Drug Discovery and Development
- National AI **I**nstitute for **F**oundations of **M**achine **L**earning
- **T**argeted **T**herapeutic Drug Discovery & Development **P**rogram
- Texas Biologics @ UT
- Researchers and physicians at **UT Austin**, **Dell Medical School**, **MDACC**, **UT Southwestern**, **UTHSC San Antonio**




- **Questions?** Contact maynard@che.uextas.edu or annalee@utexas.edu

# CENTER FOR INNOVATIVE DRUG DISCOVERY AND DEVELOPMENT

**Director: Stanton McHardy, UTSA**



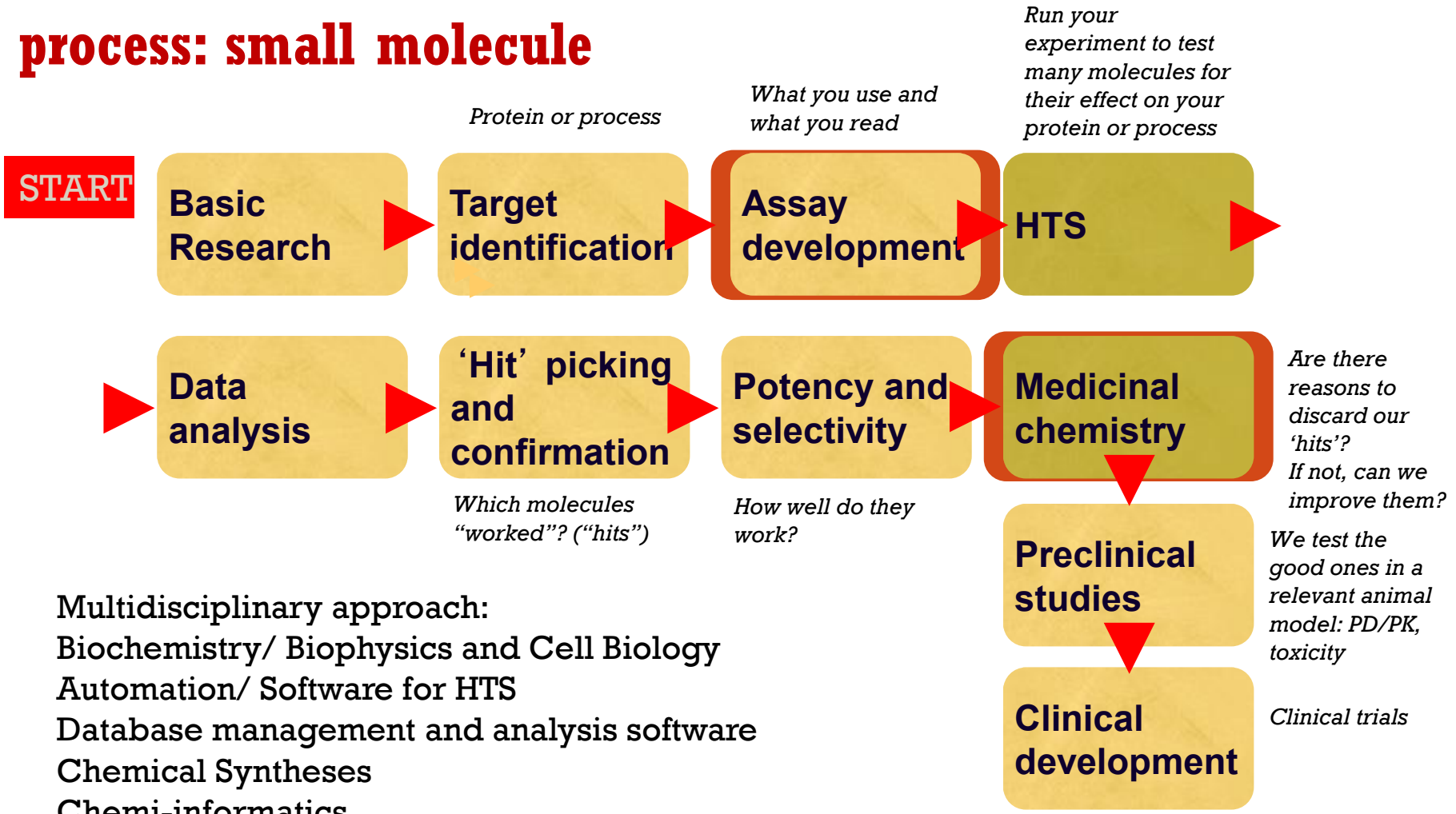

- **CIDD Med Chem and HTS Facilities**
- **X-ray and NMR Facilities and Cryo-EM**
- **GCCRI RNAi/CRISPR HTS Facility**
- **Computational Biology and Bioinformatics Initiative**

**Integration, Feed Drug and Target discovery pipelines**

# CENTER FOR INNOVATIVE DRUG DISCOVERY AND DEVELOPMENT

**Director: Stanton McHardy, UTSA**

## The HTS process: small molecule




Multidisciplinary approach:
Biochemistry/ Biophysics and Cell Biology
Automation/ Software for HTS
Database management and analysis software
Chemical Syntheses
Chemi-informatics
Animal Models

# CENTER FOR INNOVATIVE DRUG DISCOVERY AND DEVELOPMENT

**Director: Stanton McHardy, UTSA**

## Libraries at the CIDD HTS Facility

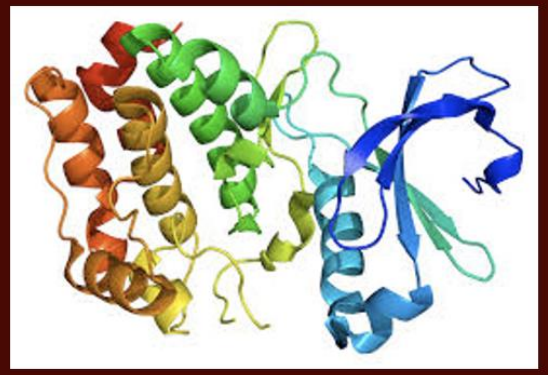
**Chemical Libraries (~171,000 total, sourced from ~2.0 million compounds):**

- LOPAC-Pharmacologically Active (1,280)
- Prestwick FDA-Approved (1,200)
- Life Chemical Bioactives (8,000)
- Maybridge HitFinder (14,400)
- Chembridge NovaCore (20,000)
- Chembridge DiverSet (30,000)
- Life Chemical Fsp3 (25,600)
- Life Chemical Diversity Set (56,000)
- UTSA Select (>2,500)
- New: Covalent Inhibitors (3508)
- New: Ion Channel Inhibitors (9000)
- **Sourcing: Macrocyclic compounds**- complex, unique chemical space, targeting protein-protein interfaces.

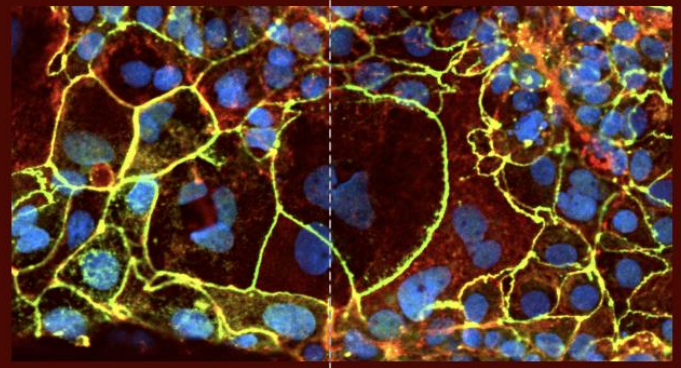
# COMBINATORIAL DRUG DISCOVERY PROGRAM

**Director: Peter Davies, TAMU IBT**

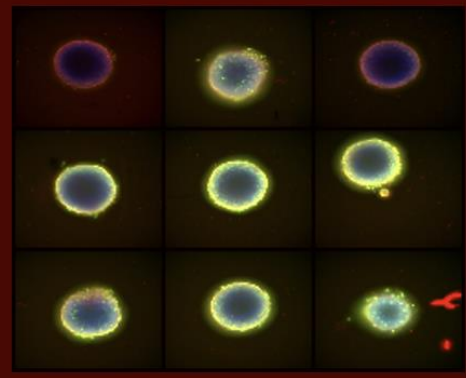
## CDDP High Throughput Screening & Imaging Model Systems



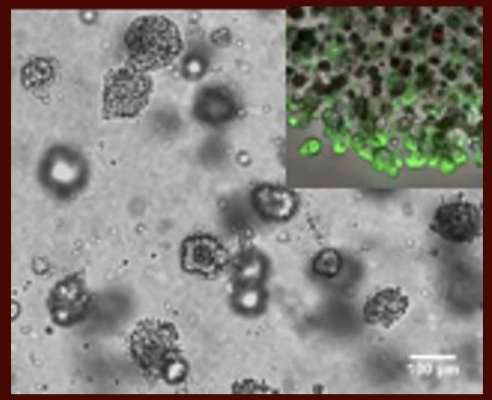
Proteins (enzymes)



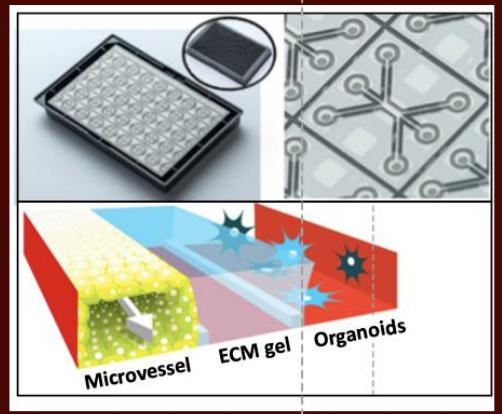
Cells



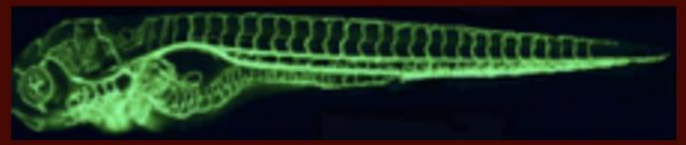
Spheroids



Organoids




Tissue Chips



Simple model organisms

# COMBINATORIAL DRUG DISCOVERY PROGRAM

**Director: Peter Davies, TAMU IBT**

## CDDP Screening Infrastructure

### Stand alone liquid handling

- Multidrops

- Multiflow

- Mantis

### Automated liquid handling platforms + TC Incubators

- Plate washers

- Tecan Evo

- Labcyte Echo

### Robotically integrated Detection systems

- ImageXpress Micro confocal & IN Cell 6000

- MP-FLIM

- ZE5 flow cytometer

- Neo Synergy2 & Tecan M1000 readers

### Data & Image processing and secondary analysis

- Biovia Pipeline Pilot
- Deep Learning Studios
- Python
- Fiji/ImageJ
- CellProfiler



# COMBINATORIAL DRUG DISCOVERY PROGRAM

**Director: Peter Davies, TAMU IBT**

## Services

- Single and combinatorial compound screening
- New drug and repurposing screens
- Focused mechanistic screening
- HT in vitro screening
- Automated HT microscopy
- MP-FLIM optical metabolic imaging
- 2D and 3D model systems

- Honest broker between company drug collections and academic models
- Experts in HT drug discovery research
- Assay development and optimization
- Biochemical and image-based temporal and end-point assays
- Develop and implement both conventional statistical and advanced machine learning models applied to HT chemical screening

# GCC CENTER FOR ADVANCED MICROSCOPY AND IMAGE INFORMATICS

**Director: Mike Mancini, BCM/TAMU IBT**

## IMAGING TEAM

Advanced Imaging Platforms

Leica SP8
STED/FLIM/FCS


Bruker
Vutara 352 STORM

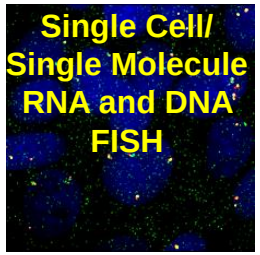
Yokogawa
CV8000
(NEW)

IncuCyte S3

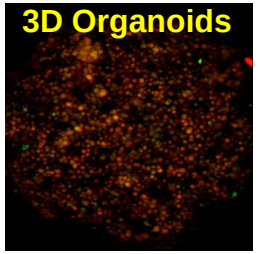
Baylor College of Medicine

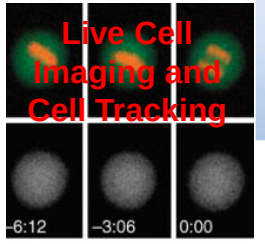
BIOSCIENCES & TECHNOLOGY

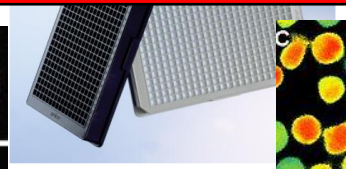


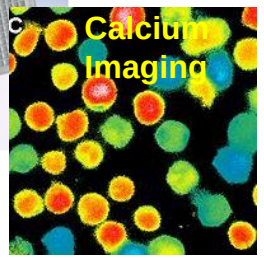

## ADVANCED IMAGING APPLICATIONS



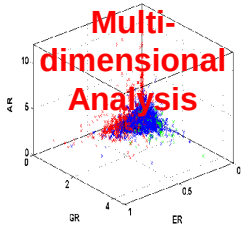



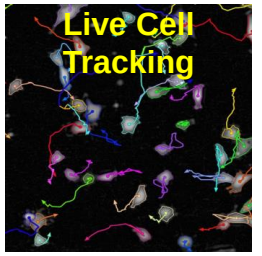
HTM

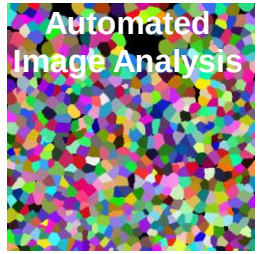


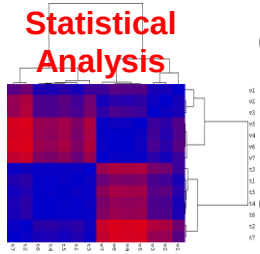

## IMAGE INFORMATICS TEAM

Advanced Image Analysis




Custom image informatics to support all levels of analysis
Software: PipelinePilot, Matlab, Python. Fiji, R

# GCC CENTER FOR ADVANCED MICROSCOPY AND IMAGE INFORMATICS

**Director: Mike Mancini, BCM/TAMU IBT**

## YOKOGAWA CENTER OF EXCELLENCE: CV8000: HIGH THROUGHPUT SPINNING DISK CONFOCAL

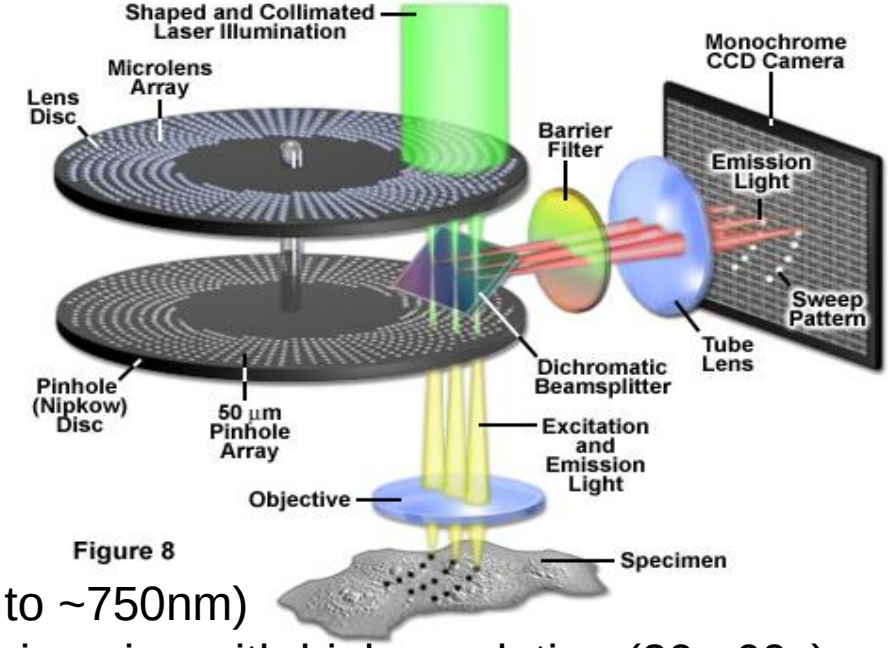
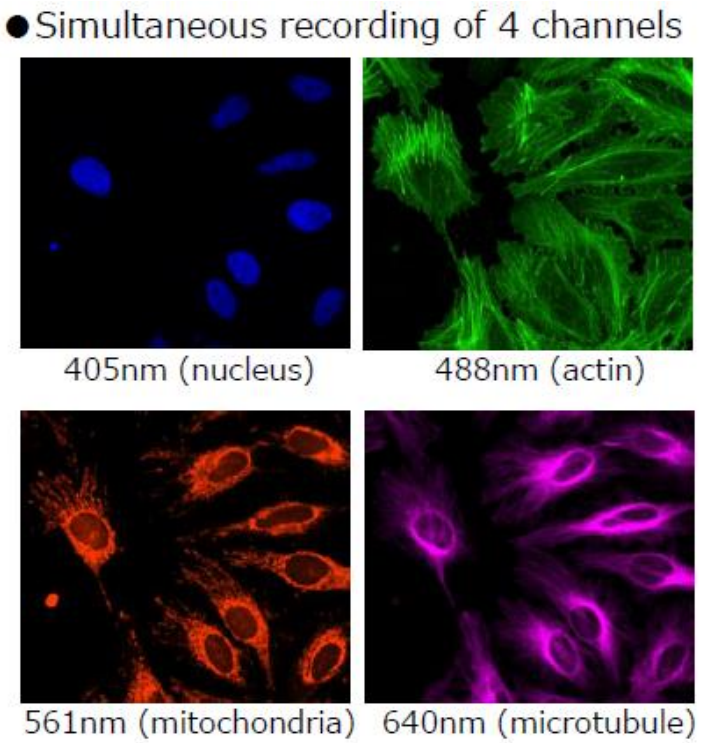



Figure 8




- 6 laser lines (from ~400nm to ~750nm)
- Water objectives for deeper imaging with high resolution (20x-60x)
- 4 cameras, allowing simultaneous collections
- Live imaging (fast acquisition for long time)
- On deck dispenser
- Fast (384 well imaging, 1 image/well) in ~4 min

# GCC CENTER FOR ADVANCED MICROSCOPY AND IMAGE INFORMATICS

**Director: Mike Mancini, BCM/TAMU IBT**

- **AREAS of interest in cancer research:**
  - Assay development for imaging-based mechanistic and/or phenotypic analyses, including HT Screening
  - 3D imaging
  - Live imaging/video analysis; short- or long-term imaging
  - White Light Laser Confocal, dial-in excitation and emission.
  - Super-resolution microscopy (SIM, STED, STORM)
  - Fluorescence Correlation Spectroscopy (FCS)
  - Fluorescent Lifetime Imaging Microscopy (FLIM)
  - Phenotypic heterogeneity/spatial analysis
  - Novel imaging-based hybridoma screening
  - **Benefits: only cost is experiment specific reagents and consumables!**

# GCC CENTER FOR COMPREHENSIVE PK/PD AND FORMULATION

**Director: Dong Liang, TSU**

## FORMULATION DEVELOPMENT

### Pre- and Formulation

**1. Drug Characterization**
- Solubility
- pka
- Log P
- Stability

**2. Basic Formulation:**
- Cosolvent
- Cyclodextrin
- Dispersed systems

**3. Advanced Drug Delivery:**
- Micro/nanoemulsions
- Liposomes
- Nanoparticles

## PK/PD CHARACTERIZATION

### Pre-clinical PK/PD Evaluations

**4. Bioanalysis**
- Method development and validation to quantitate concentrations of drug or metabolite in biological matrix
- Identification of unknown metabolites using accurate mass

**5. In Vitro Metabolism**
- Drug metabolism characterization using tissue microsomes, S9 fraction, and Recombinant enzymes
- Metabolite profiling & identification

**6. In Vitro Biopharm Characterization**
- Membrane permeability and transporter identification
- Bindings to plasma proteins, albumin or α-glycoprotein

**7. In Vivo PK**
- PK studies in rats and mice after IV, oral, IP and SC drug administration
- Dose linearity PK studies
- Bioavailability studies
- PK studies on tissue distribution

**8. In Vitro/In Vivo PD**
- Cell proliferation assay
- Apoptosis assay
- DNA damage assay
- Migration/invasion assays
- Xenograft assay
- Biomarker assays on tumors from xenograft models
- Genetic mouse models for PD assays

**9. PK/PD Modeling and Simulation**
- Consultation on experimental design
- PK modeling development and simulation
- PD modeling and determination of parameters
- PK/PD modeling

CENTER FOR COMPREHENSIVE PK|PD + FORMULATION

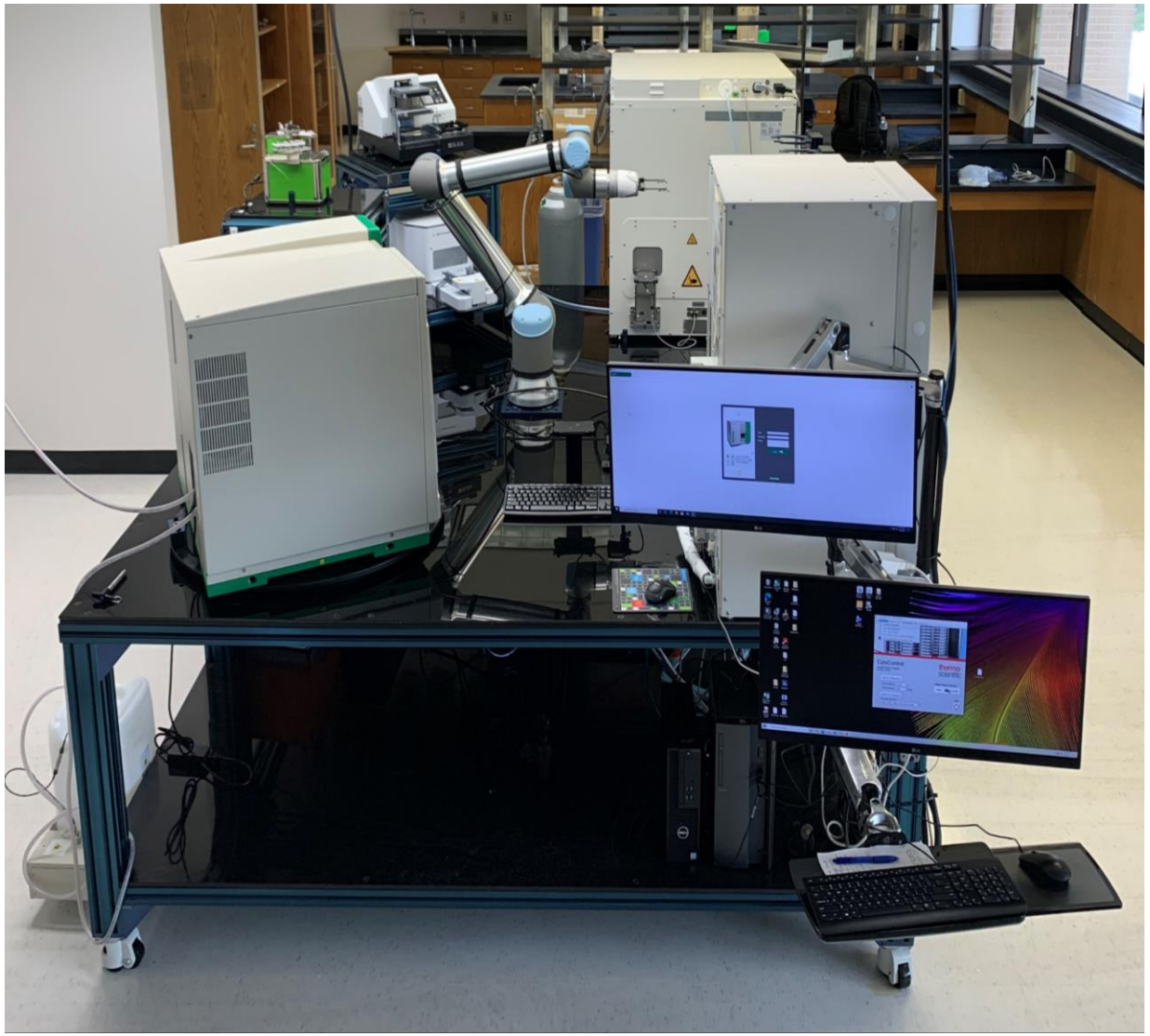
# GCC HIGH THROUGHPUT FLOW CYTOMETRY

**Director: Margie Moczygembe, TAMU IBT**

## HIGH THROUGHPUT FLOW CYTOMETRY PROGRAM FOR DRUG SCREENING

- Institute of Biosciences and Technology, Texas A&M HSC

# GCC HIGH THROUGHPUT FLOW CYTOMETRY



**Director: Margie Moczygembe, TAMU IBT**

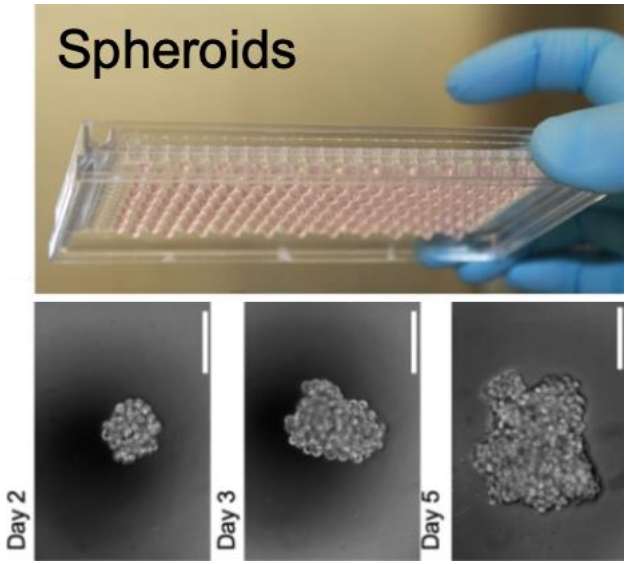
**Services provided with automated HT flow cytometry for drug discovery:**

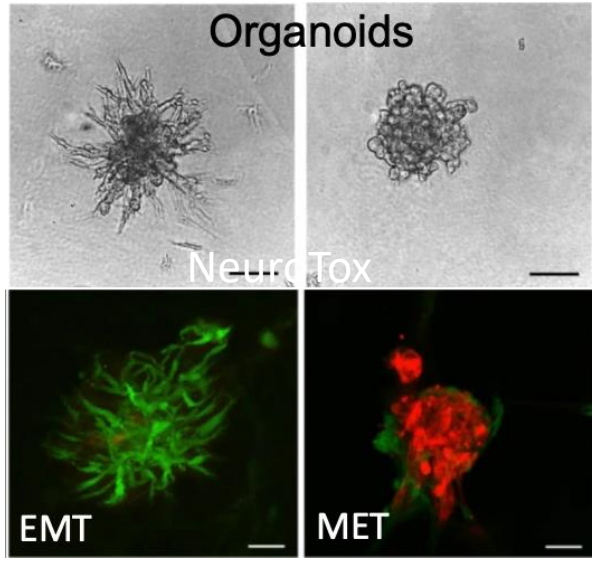
- HT drug screening in hours vs days (speed)
- Large scale screens; ability to analyze hundreds to thousands of samples (scalability)
- Offer various FDA approved and mechanistically annotated drug libraries (customized projects)
- Ability to multiplex; high content platform generates lots of data
- Detection of extracellular vesicles, exosomes, and nanoparticles with small particle detector on BioRad ZE5 cell analyzer
- Informatics analysis with machine learning
- Pharmacogenomics
- Affordable (cost effective)

# GCC MICROPHYSIOLOGICAL LEAD OPTIMIZATION AND TOXICITY SCREENING

**Director: Cliff Stephan, TAMU IBT**

- A unique core facility providing both tumor efficacy testing and safety pharmacology profiling in complex in vitro 3D models at a level of throughput that can support lead optimization of drugs and drug combinations
- Assay design, development, and optimization of complex 3D in vitro models for high throughput screening
- Access to 3D microfluidic testing platforms (e.g., tissue- and tumor-on-a-chip platforms, tumor organoid and spheroid culture systems)
- Evaluating the efficacy and toxicity liability profiling (cardio, CNS, liver) for lead optimization campaigns

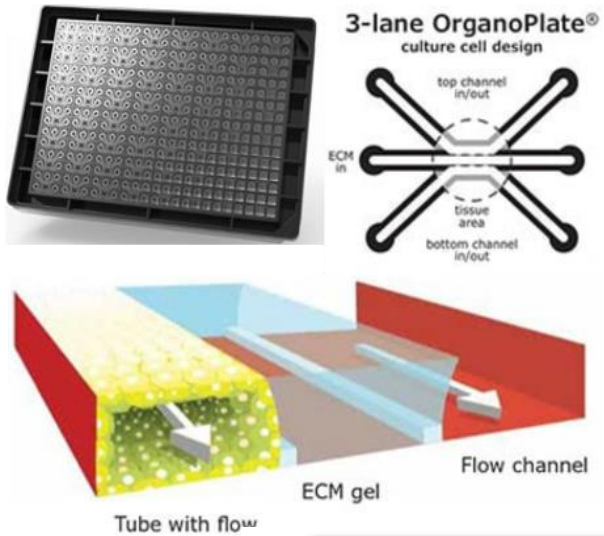


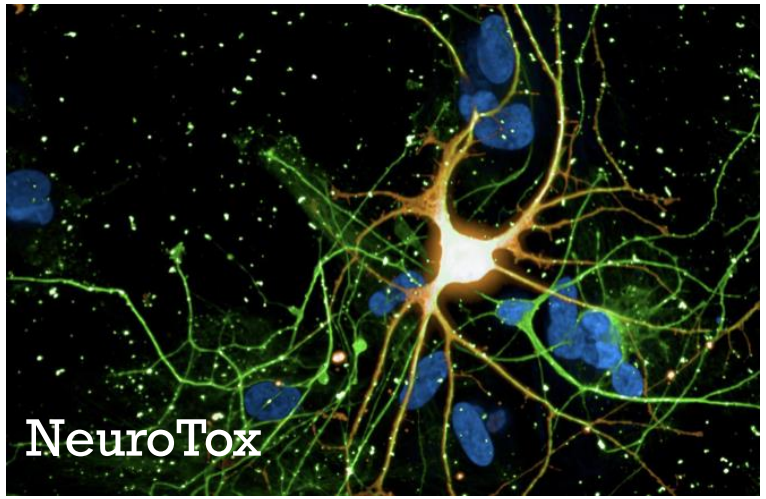
# GCC MICROPHYSIOLOGICAL LEAD OPTIMIZATION AND TOXICITY SCREENING

**Director: Cliff Stephan, TAMU IBT**

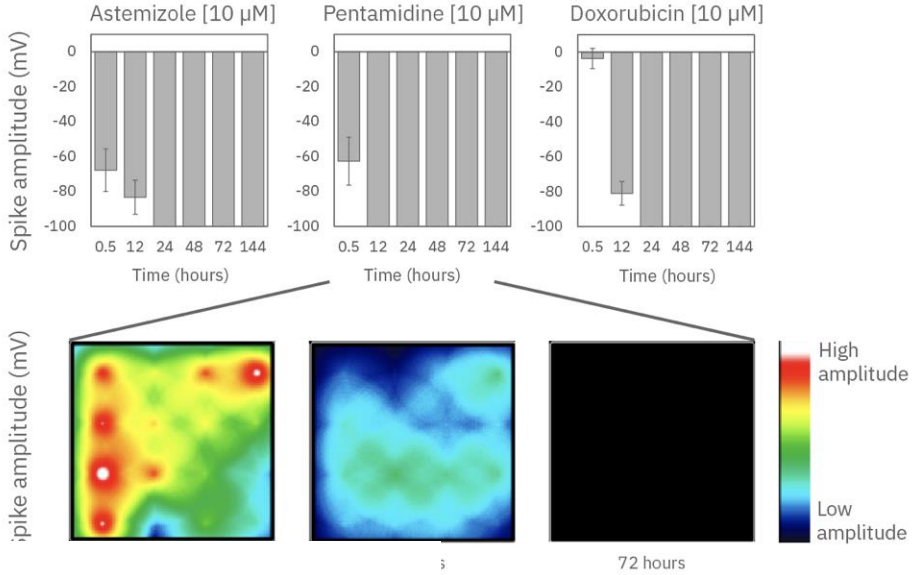
## Microphysiological Platforms




## Lead Op Tox Profiling




## Cardiotox




CPRIT-Funded Drug Discovery and Development Pipeline

**Target Identification & Hits Discovery/New Leads**

- TAMU/BCM – Advanced Microscopy
- UT San Antonio – Medicinal Chemistry
- UT Austin – Chem-Informatics/Modeling
- Baylor Col. Med. – DNA encoded Library
- TAMU – Combinatorial Repurposing
- TAMU – HT Flow Cytometry

**Lead Optimization & Safety**

- MLOTS In vitro Efficacy Testing and Toxicity Screening

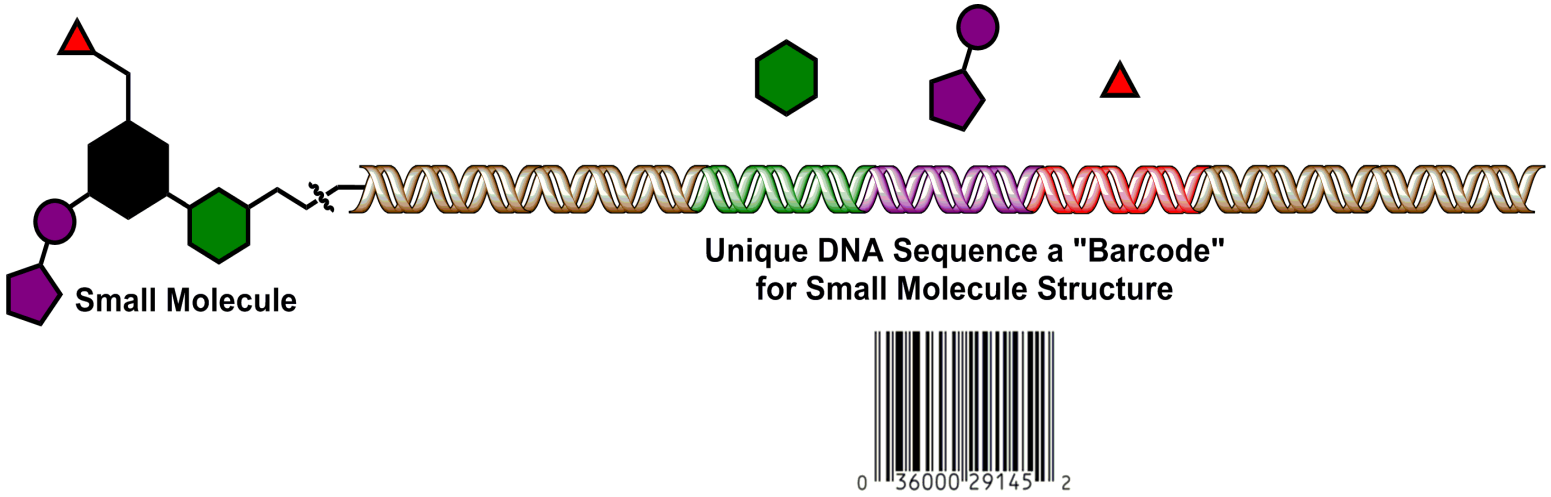
**Pre-Clinical & Clinical Testing**

- Texas Southern – Drug Formulation and PK/PD Testing
- TMC Fdn – Business-Driven Accelerator for Cancer Therapeutics

# PRECLINICAL CANDIDATE DISCOVERY CORE; CENTER FOR DRUG DISCOVERY

**Director: Martin Matzuk, BCM**

## DNA-ENCODED CHEMISTRY TECHNOLOGY (DEC-TEC)

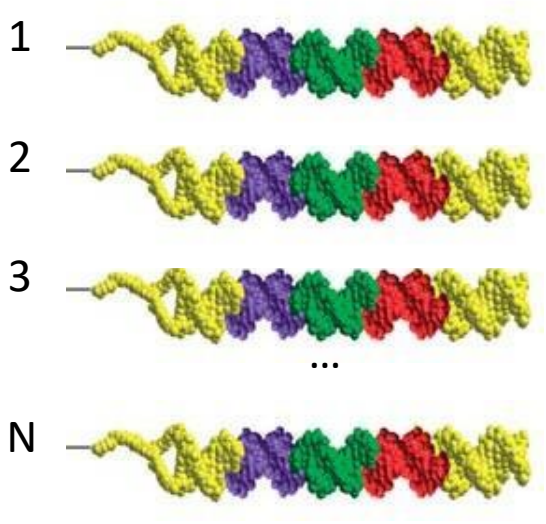


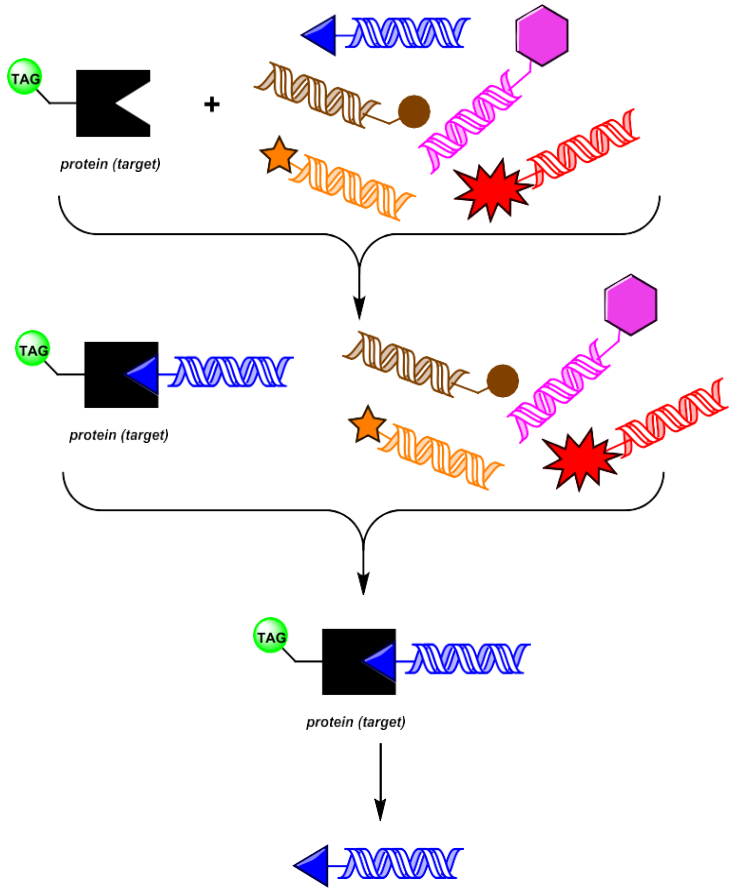

- Synthesize **BILLIONS** of **drug-like molecules** via combinatorial chemistry
- Unique **DNA "barcodes"** enable screens of complex mixtures
- Screen pooled compounds for binding affinity, and then sequence DNA
- Enables wider, cheaper screens than HTS

# PRECLINICAL CANDIDATE DISCOVERY CORE; CENTER FOR DRUG DISCOVERY

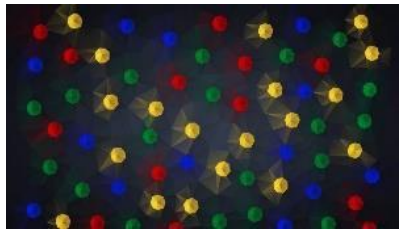
**Director: Martin Matzuk, BCM**

## DISCOVERY PROCESS




Courtesy of Illumina, Inc.



**Prepare library (~$10^8$ structures)**

**Affinity Selection (~$10^8$ molecules)**

**Sequence DNA (~$10^8$ sequences)**

# TARGETED THERAPEUTICS DRUG DISCOVERY AND DEVELOPMENT PROGRAM

**Director: Kevin Dalby, UT Austin**

Project consultation and education, grant/manuscript support, and staff-assisted support in:

- Compound screening
  - Biochemical, cell-based, design optimization
  - Small molecule preliminary and follow up screening
- Medicinal chemistry
  - Structure-guided synthesis of new analogs
  - Scale-up synthesis for lead progression
- Chemoinformatics and modeling
  - Preliminary SAR for hits
  - Identification of commercially available analogs
  - Advanced in silico modeling and early prediction of ADMET properties
- Lead characterization
  - Structural biology: x-ray crystal structures of target-inhibitor complexes
  - PK studies: formulation and evaluation of in vivo compound bioavailability

# TARGETED THERAPEUTICS DRUG DISCOVERY AND DEVELOPMENT

**Director: Kevin Dalby, UT Austin**

## Resources

- **Detection**
  - Synergy Neo2 and H4 plate readers
  - Cytation 5 cell imaging plate reader
  - Envision Plate Reader
  - FlexStation 3
  - IncuCyte Zoom System – RT live cell analysis
  - J-815 CD spectrometer
  - Cary 4000 UV-Vis
  - Biacore S200
- **Liquid Handling**
  - Echo 550 acoustic liquid handler
  - Janus automated workstation
  - Microflo select bulk liquid dispenser
  - EL405lx plate washer
- **Tissue Culture**
  - Forma 3110 CO2 Incubator, Leica DMi1 microscope (4x, 10x, 20x), biosafety hood, centrifuge, water bath
- **Computing facility**
  - Computing cluster
  - GPU computing cluster
  - High performance computing cluster
  - Workstations
- **Software**
  - CDD, Daylight Reaction Toolkit, ROCS, EON, OpenEye, GOLD, GLIDE, Amber, GROAMCS, TINKER, OpenMM, Pymol, VMD, Chimera
- **Medicinal Chemistry**
  - CEM Liberty microwave peptide synthesizer
  - MiniBlock synthesizer and Minimapper liquid handler
  - Rotavapor RII
- **Screening capability**
  - 96,384,1536 well/end-point and kinetics
  - Readout type: Abs, FI, TRF, FRET, BRET, FP, Lum, Lance, Alphascreen, Cellular imaging (DAPI, GFP, RFP, CFP, Texas red; 4x, 10x, 20x, 40x), Thermal melting (Tm), Circular Dichroism (CD), Spectra/well area scan

# TARGETED THERAPEUTICS DRUG DISCOVERY AND DEVELOPMENT

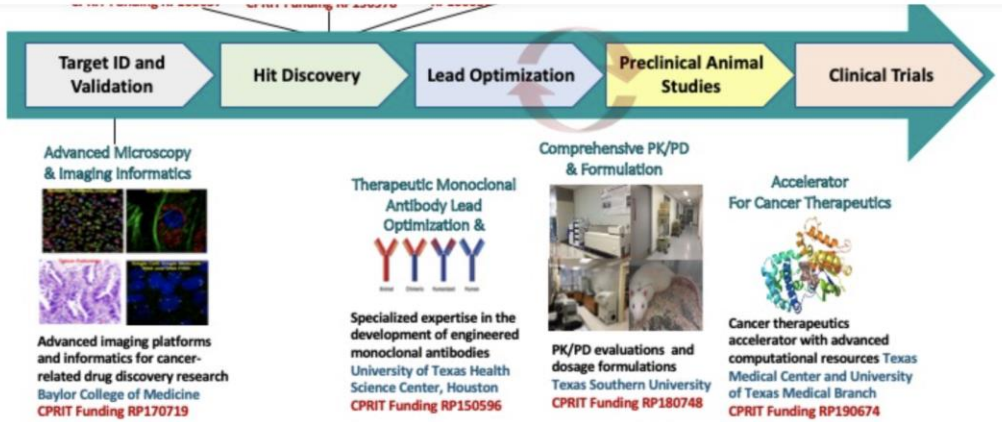
**Director: Kevin Dalby, UT Austin**

## Renewed in 2021 with expansion

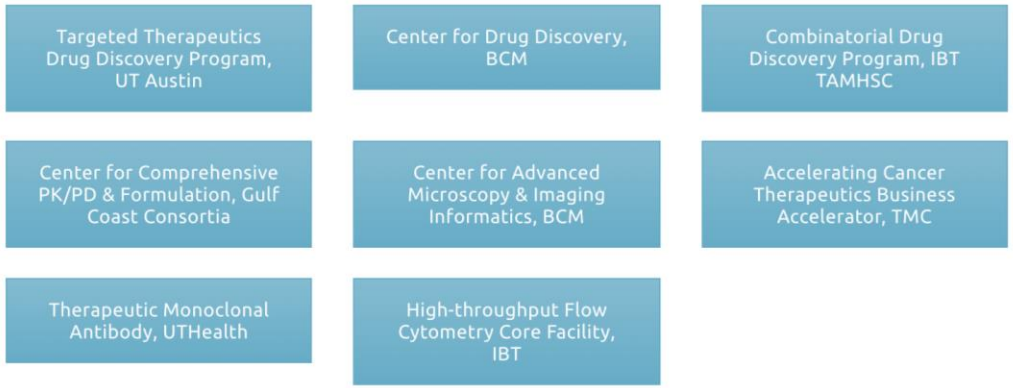
- Continuation of small molecule screening and medicinal chemistry
- New platforms for production of cancer-related recombinant proteins from mammalian cells and SPR-based biophysical screening
- New cancer-related drug discovery program based on the application of targeted protein degradation via Proteolysis Targeting Chimeras (PROTACs) to identify clinically relevant drugs
- Expanded educational program

# GULFCOASTCONSORTIA.ORG

**Research → Drug Disc/Dev → Shared Core Network**



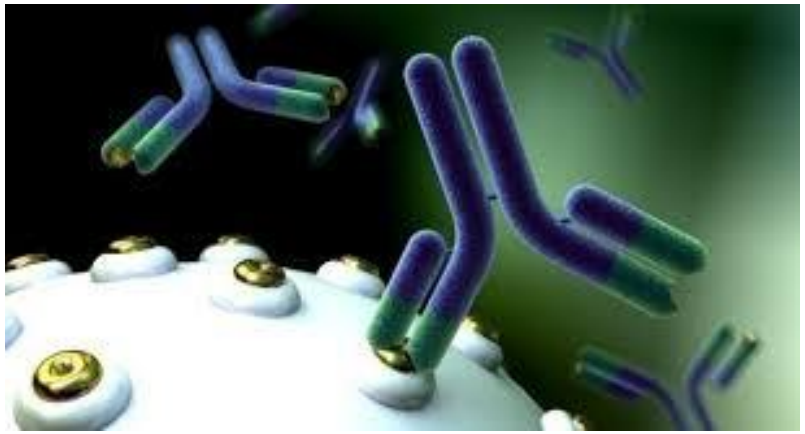




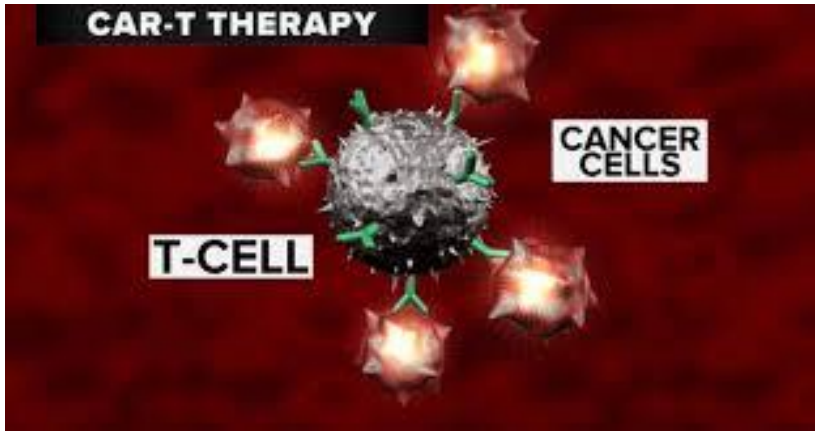

**GCC MOU for shared resources**

# ADVANCED CANCER ANTIBODY DRUG MODALITIES CORE

**Director: Zhiqiang An, UTHealth**

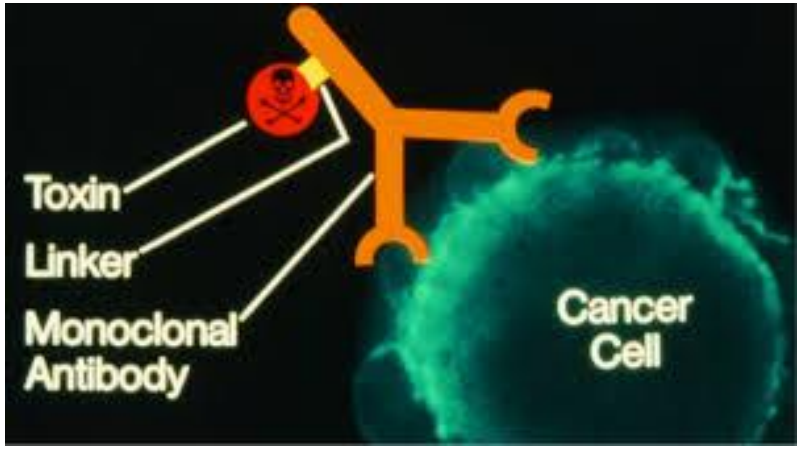


**Monoclonal Antibody**

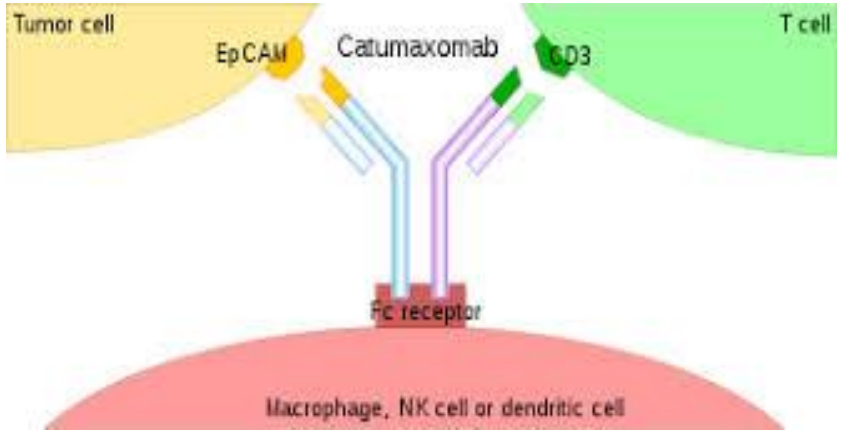



**CAR-T Cell Therapy**

## *ANTIBODY-BASED DRUG MODALITIES*




**Antibody Drug Conjugate**




**Bispecific Antibody**

# ADVANCED CANCER ANTIBODY DRUG MODALITIES CORE

Director: Zhiqiang An, UTHealth

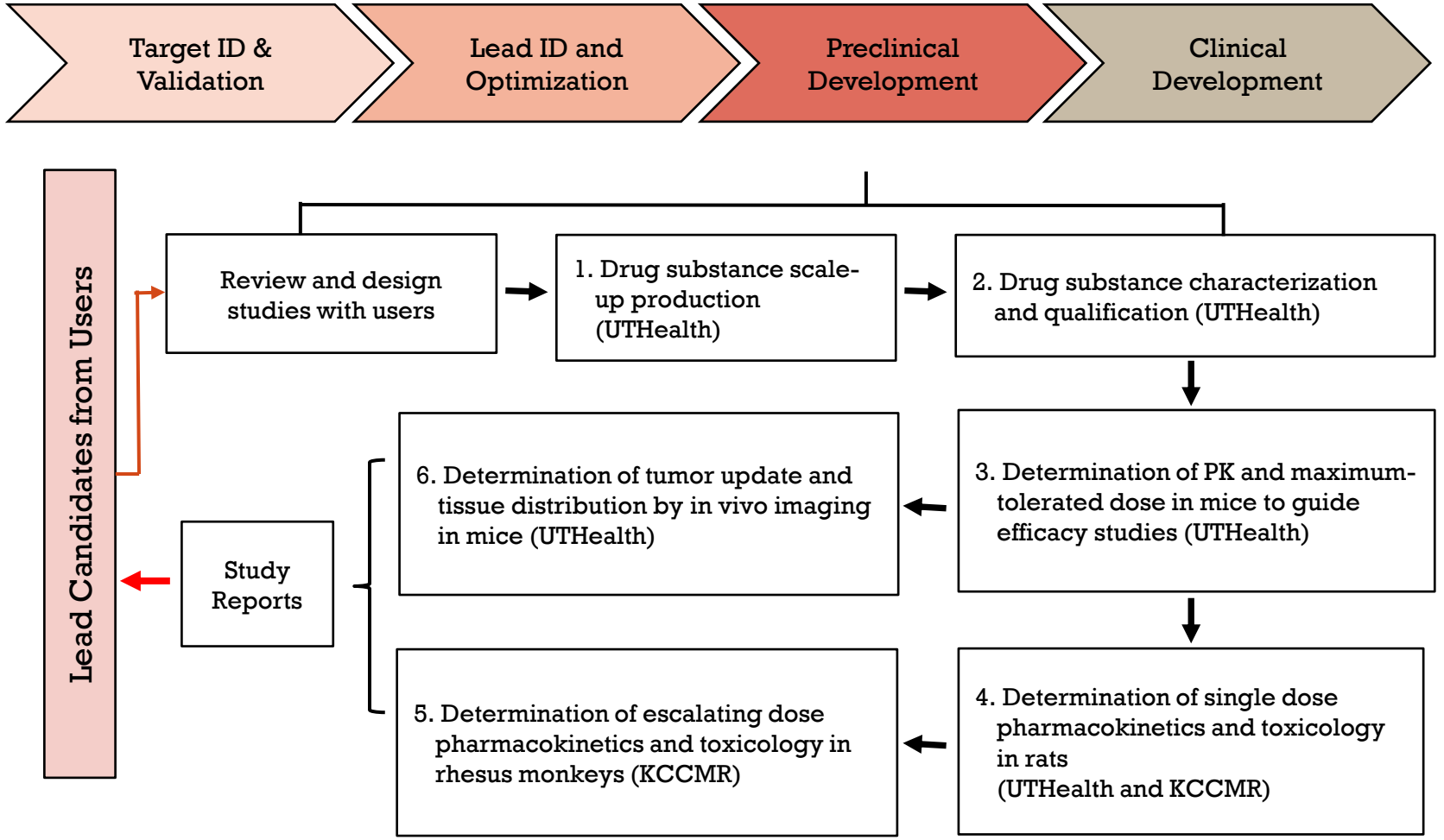
## Antibody Technologies

- mAbs from immunized animals (rabbits, mice, rat)
- mAbs from plasma B cells
- mAbs from memory B cells
- mAbs from phage libraries
- Bispecific mAbs
- ADCs
- CAR-T

- Stable CHO cell lines for antibody expression
- Antibodies crossing the BBB
- Generation of synthetic nanobody library using phage display
- Antibodies targeting complex membrane proteins
- Preclinical PK and tox

# PRECLINICAL DEVELOPMENT CORE FOR LARGE MOLECULE THERAPEUTICS

**Director: Qingyun "Jim" Liu, UTHealth**



# PRECLINICAL DEVELOPMENT CORE FOR LARGE MOLECULE THERAPEUTICS

**Director: Qingyun "Jim" Liu, UTHealth**

- Drug candidate criteria:
  - Robust anti-tumor efficacy in vivo.
  - Candidate will be evaluated by core investigators for acceptance.

- Key capabilities:
  - Scale up production and characterization of antibodies and other large molecule drug candidates.
  - Pharmacokinetic and toxicology studies in rats and rhesus monkeys.
  - Whole body imaging studies in mice

- **No charge to investigators for accepted drug candidates**