Progress on 21st Century Toxicology and Risk Assessment at US EPA

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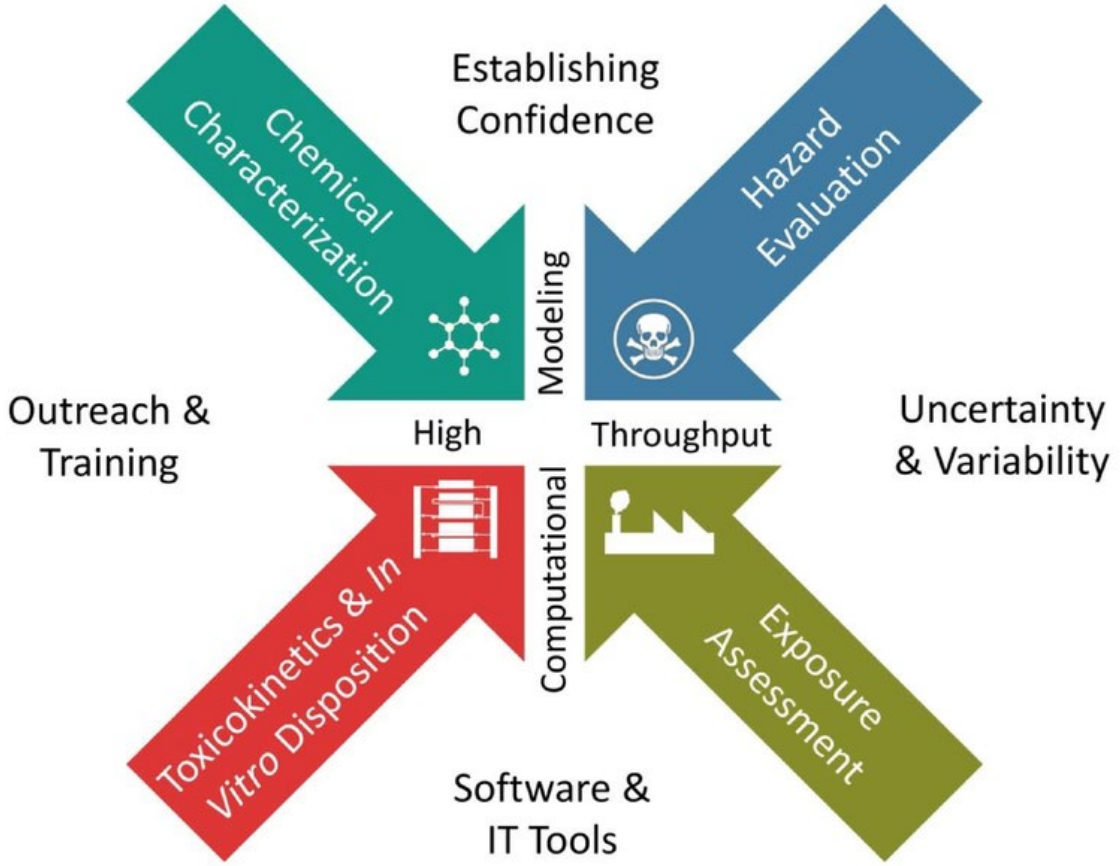
- Publications
  - 246 CCTE-led or contributed since March 2019
  - 102 in 2020, 92 in 2021

- Highlights for today
  - NAMs for organ toxicity
  - Toxicokinetics
  - Value of information framework for chemical toxicity testing using NAMs



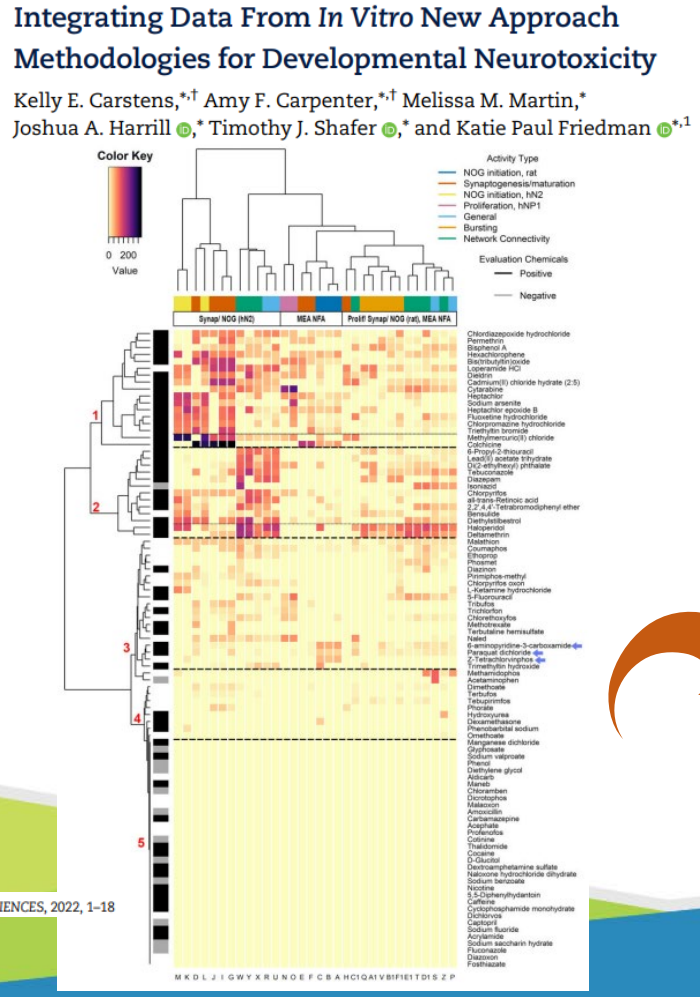
RS Thomas et al. Tox Sci 2019: June 1; 169(2):317-332

In Vitro High-Throughput Capacity Building

Developmental Neurotoxicity

Data Integration

Calculating a selectivity metric at sub-cytotoxic doses is informative for identifying patterns of biological activity.



Establishing Methods

Establishing methods for the community to facilitate assay standardization and adoption.

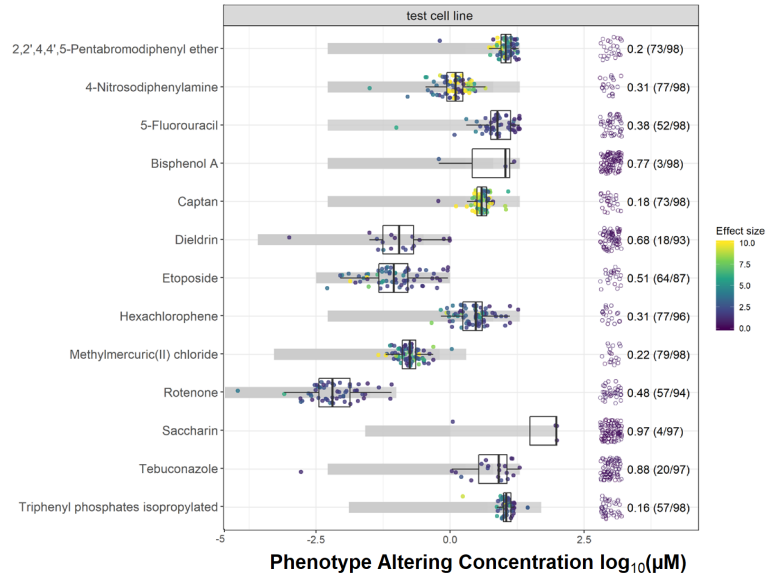
"Assessment of Larval Zebrafish Locomotor Activity for Developmental Neurotoxicity Screening" in Experimental Neurotoxicology Methods (Stephanie Padilla; July 2021).

"Using Zebrafish to Assess Developmental Neurotoxicity" in Reproductive and Developmental Toxicology (Stephanie Padilla; June 2022).

OECD DNT Expert Group
Guidance on evaluation of data from the developmental neurotoxicity in vitro testing battery (Target 2022 publication)

Genetic Susceptibility

Genetic diversity across cell lines enables determination of inter-individual variability in biological potency.



Tox21 Cross-Partner Project lead by EPA, NTP, FDA
Cell painting / high content imaging in 98 Diversity Outbred neural progenitor cell lines [unpublished data]

In Vitro High-Throughput Capacity Building

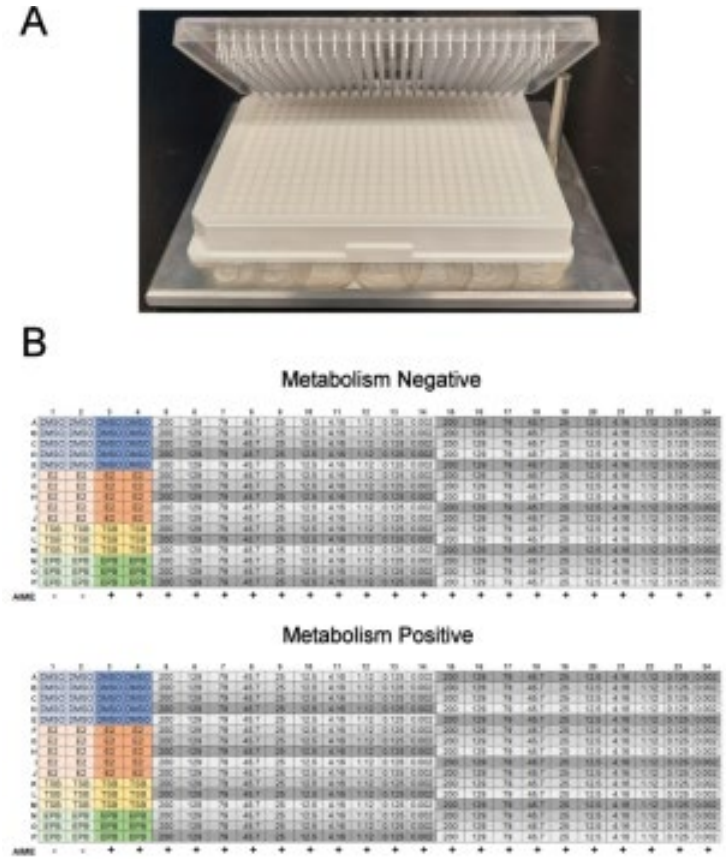
Endocrine Disruption

Profiled chemicals associated with ERTA identified routes of transformation and metabolites assoc'd with estrogenic FX.

› Toxicol Sci. 2022 Feb 16;kfac019. doi: 10.1093/toxsci/kfac019. Online ahead of print.

Chemical Screening in an Estrogen Receptor Transactivation Assay with Metabolic Competence

Kristen Hopperstad [1], Danica E DeGroot [1], Todd Zurlinden [1], Cassandra Brinkman [1], Russell S Thomas [1], Chad Deisenroth [1]



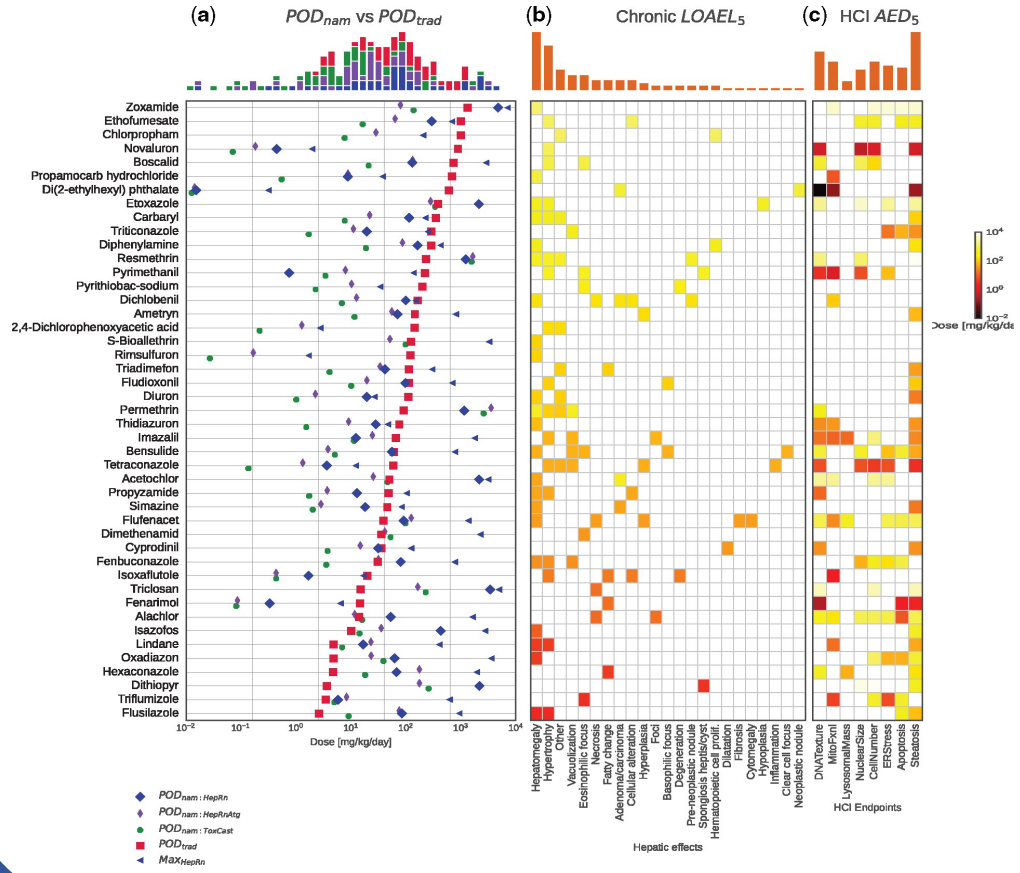
Hepatotoxicity

NAMs based on the same species and cell type as the adverse outcome may produce estimates closer to the traditional in vivo POD.

Estimating Hepatotoxic Doses Using High-Content Imaging in Primary Hepatocytes

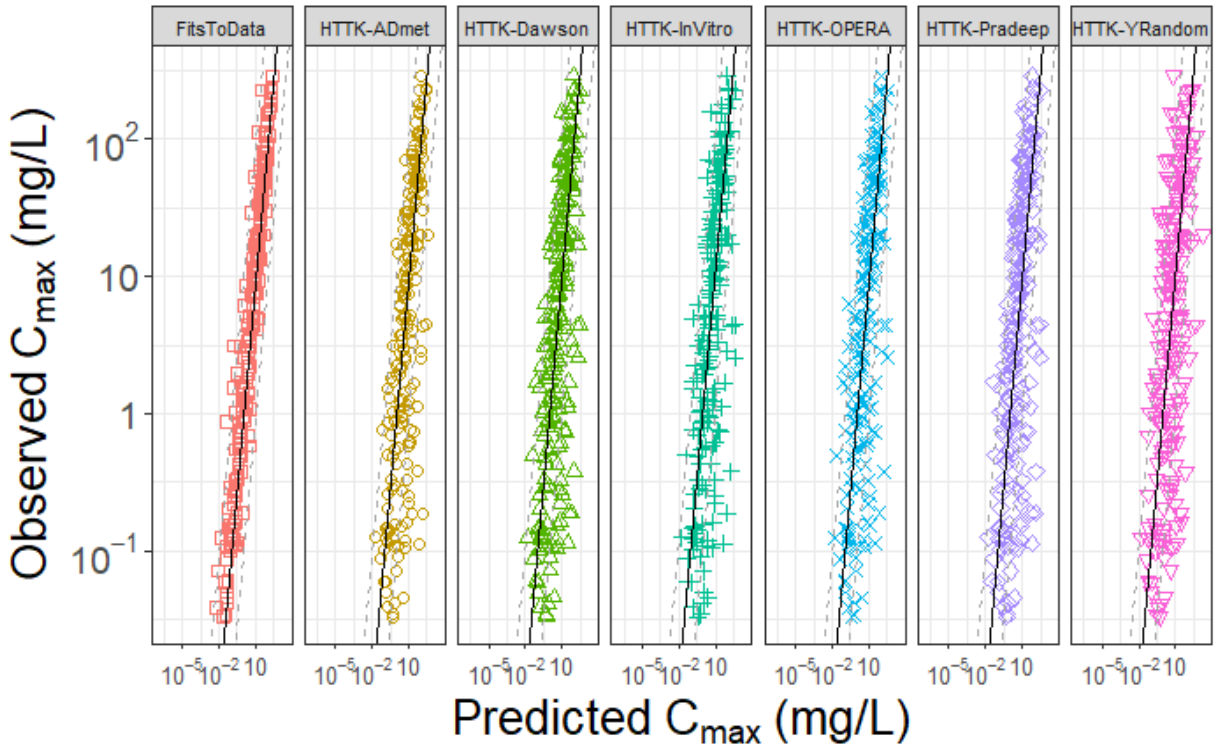
Imran Shah ✉, Todor Antonijevic, Bryant Chambers, Joshua Harrill, Russell Thomas

Toxicological Sciences, Volume 183, Issue 2, October 2021, Pages 285–301,



QSPRs (Quantitative-Structure Property Relationships) for HTTK (High Throughput Toxicokinetics)

- >1000 non-pharmaceutical chemicals now have in vitro TK data after over a decade of research.
- **For sufficiently similar chemicals, we may not always need to measure TK.**
- EPA is leading a collaborative evaluation of various QSPRs trained to both pharma and non-pharma chemicals for predicting HTTK.

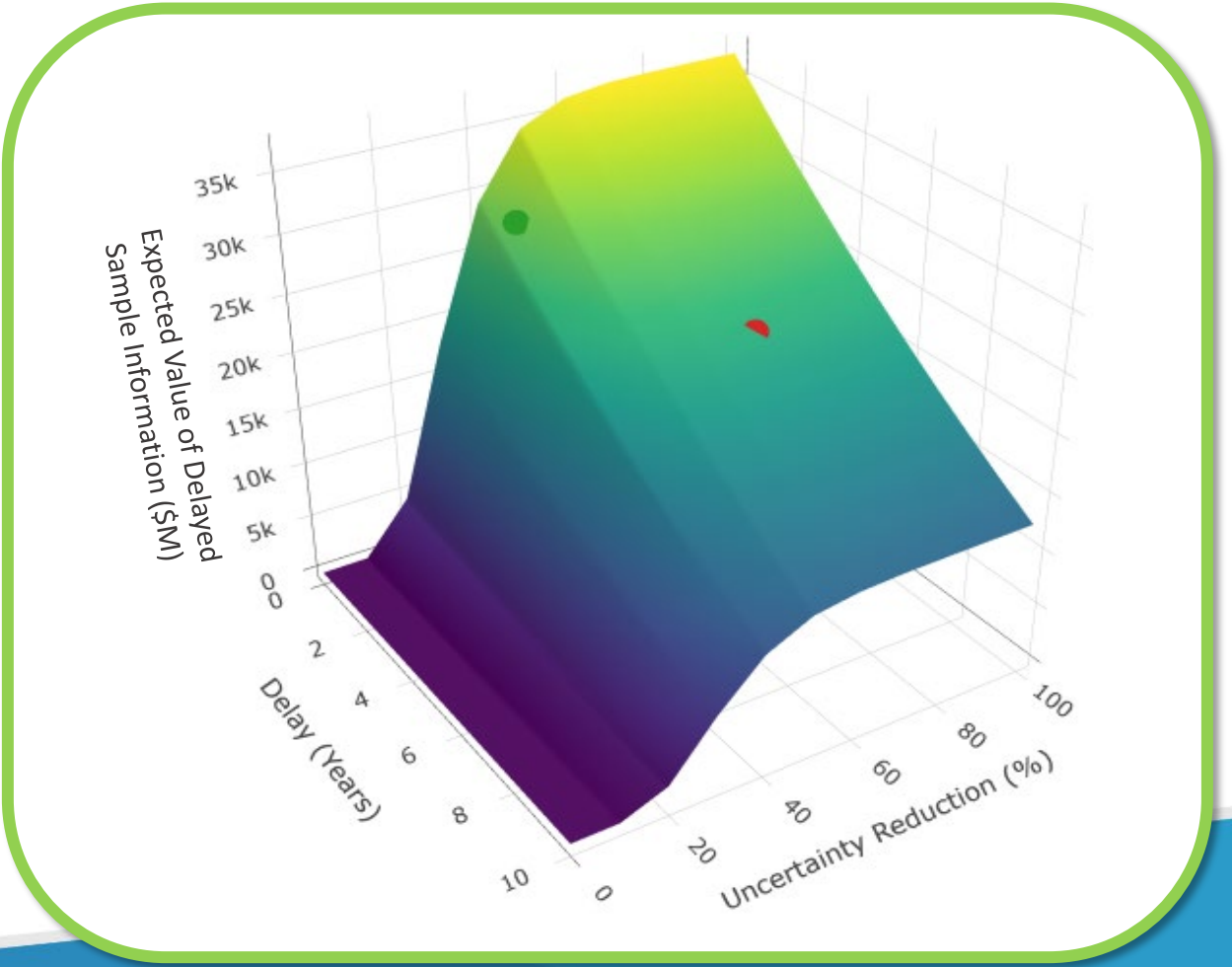


- Modeled ~90 chemicals with *in vivo, in vitro*, and *in silico* TK information across QSPR methods.
- Best predictions with fits to actual *in vivo* data, and the worst when you randomize in vitro TK (httk) data, but the separation between those extremes is small.
- Both *in vitro* measurements and open source in silico models are viable options for predicting *in vivo* TK. [John Wambaugh et al. , manuscript in preparation]

Value of Information

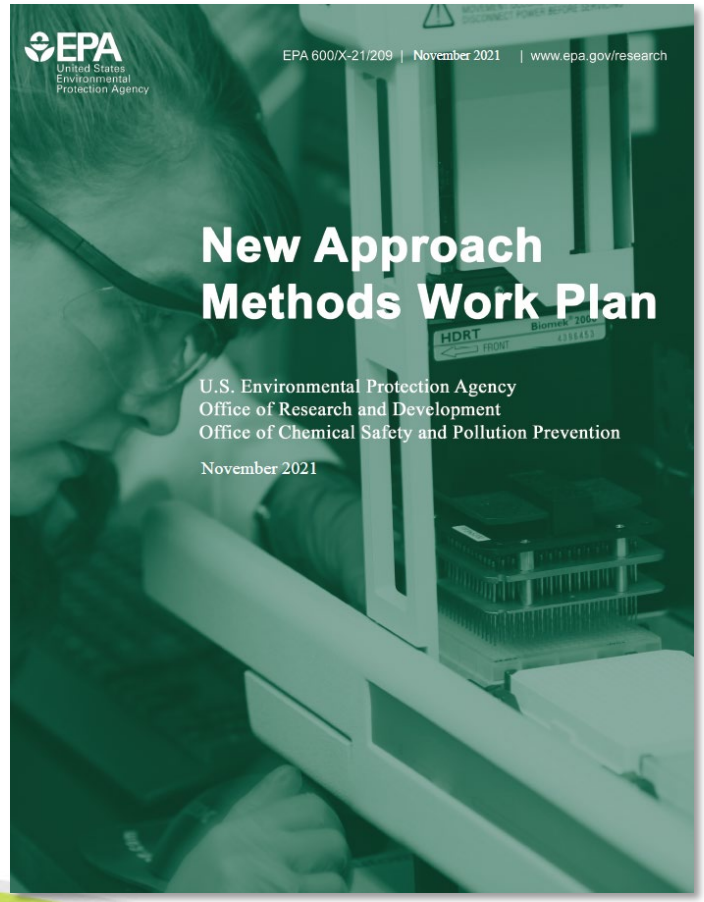
- Developed an analytical framework for evaluating the trade-offs of timeliness, cost, and uncertainty reduction associated with different toxicity testing methods in risk-based decision making.
- **Timeliness of information collection** has a significant positive impact on estimates of the VOI of chemical toxicity tests, even in the presence of smaller reductions in uncertainty.
- The positive impact of the shorter tests may be multiplicatively amplified by the ability to test more chemicals.

Trade-Offs of Uncertainty and Time of Hypothetical Toxicity Testing Methods
(Chronic Effect, Target Risk Decision Maker)



Hagiwara et al., *Risk Anal* (accepted)

Release of Updated EPA NAM Work Plan



- Expansion of the species to include all vertebrate animals to be consistent with TSCA.
- Revised deliverable timelines through 2024 that reflect the expansion of covered species and incorporate feedback received over the preceding years.
- Updated scope of the NASEM study to include a review of validation and scientific confidence frameworks for NAMs in addition to evaluating the variability and relevance of existing mammalian toxicity tests.
- Two new case studies for building confidence and demonstrating application of NAMs.
- Pilot study to develop NAMs training courses and materials

Acknowledgements

EPA Colleagues:
- CPHEA
- CEMM
- OCSPP
- OLEM
- Regions

Collaborative Partners:
- NTP
- FDA
- NCATS
- Health Canada
- ECHA
- JRC
- EFSA
- A*STAR

CCTE is comprised of over 300 scientists, staff, and contractors located in 6 U.S. locations.