DALRIADA
TURN-KEY™
DRUG DISCOVERY

Unlocking Covalent Discovery Programs Concept to PDC

Summary Deck

World-leading Covalent Capabilities

Deep covalent discovery expertise from target validation, Hit ID, H2L and Lead Op

Target-oriented *in Vitro* Covalent Discovery

- 10,000 cpd/week high-throughput covalent screening (IMA)
- Intact mass analysis (IMA) with detergent samples
- Peptide mapping analysis (PMA) follow-up site detection
- Protein scrubs generation
- 10,000 cpd/week intrinsic reactivity profiling (various nucleophiles)
- $1.4 M of globally accessible covalent compounds; Curated 100K of lead like diversity screening set; curated 1K of diversity fragment set In-house covalent library;
- GSH/GST; plasma, whole blood, hepatocytes (human, dog, murine)
- k_{inact}/K_I high-throughput determination
- Multiple orthogonal methods for kinetics and binding
- Covalent crystallography
- Multiple clinical and preclinical benchmarks profiled for reference
- Cell profiling; wash-out, protein half-life; target engagement and selectivity in chemoproteomics
- Covalent CADD capabilities

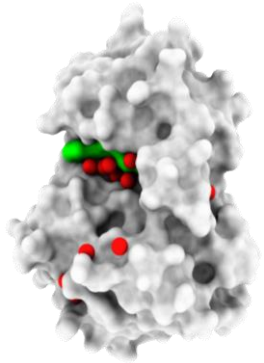
- **Expert team who prosecuted >20 covalent discovery programs**
- Top industry insight on the covalent DC and TP profiles, Hit-finding strategies, solving selectivity and metabolic stability challenges

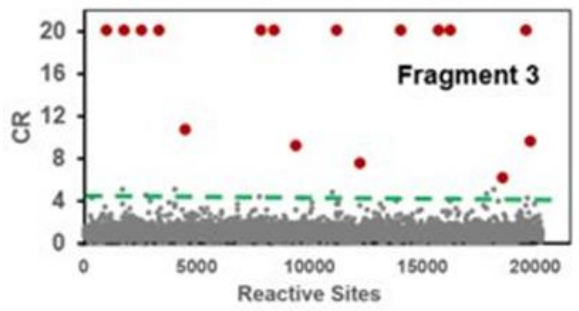
Proteome-Wide Covalent discovery

- **51,000 sites/10,500 proteins**, 13,000 proprietary sites/430 proteins & growing; proprietary ligandable site dataset
- Cysteome, and beyond
- Oncology, CNS, immunology
- In-house proteomics hit-finding library – 100 compounds*
- Curated database of sites/targets liganded in literature
- Ultra-deep target-hit profiling
- High-throughput screening
- Targeted proteomics (low-abundance sites)
- Lead covalent selectivity profiling (proteome-wide)
- Proprietary high-throughput data processing & pocket mapping algorithms

X-Valent Discovery Platform to Candidate: Covalent Drug Cascades

Unlocking holy-grail targets to small molecule therapies
Identifying novel targets ideally positioned for covalent therapeutics





- **Proprietary**, cutting-edge covalent drug discovery engine – powered by *X-valent* chemoproteomics and *X-valent* target discovery workflows
- **Proteome-wide** screening (target-directed and target-agnostic)
- Target-oriented **high-throughput** workflows
- Identification of **cryptic pockets** on desired targets
- **In-cell, accelerated**, Hit and Lead generation for **novel targets** tractable to covalent modulation
- Complete **integrated** workflow for covalent drug discovery to Candidate nomination
- World's top **expert** team in covalent drug discovery

X-Valent Screening Platform to Candidate: Covalent Drug Cascades

- Our covalent screening cascade has a strong track record of bringing discovery programs to development candidate stage.

Target Binding Time dependent; orthogonal	IMA	GSH stability	Cellular Target engagement
TI / Selectivity	PMA	GSH/GST stability	Cell Viability Two different cell lines
Crystallography	hWB stability	In vitro washout	k_{inact}/K_I
	Chemoproteomics		
h,m LM and Hep	*Solubility*	*Log D*	*Caco-2*

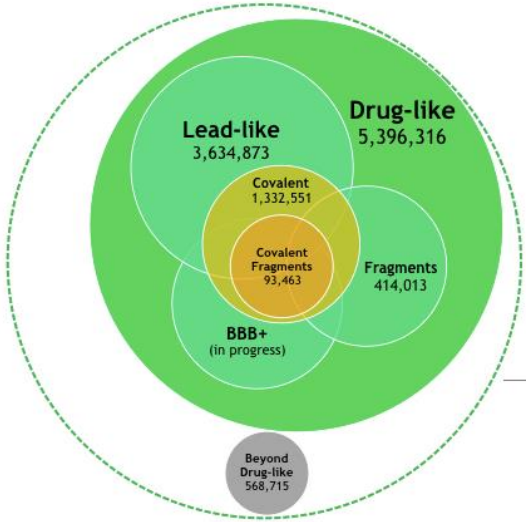
- GSH and hWB stability benchmarked versus known, marketed drugs
- GSH/GST stability vs GSH alone provides further information.
- *In vitro* washout experiments help inform duration of action, protein resynthesis and predict in vivo requirements
- LM and Hep stability (Met ID) also help prioritize compounds

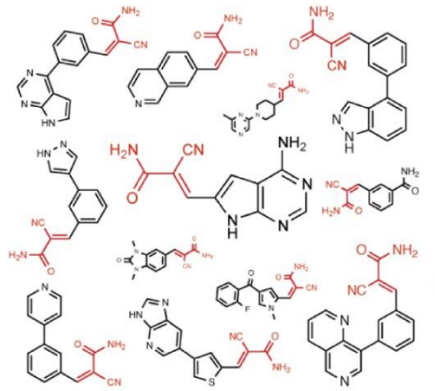
Covalent Virtual Screening

Biophysical/Biochemical

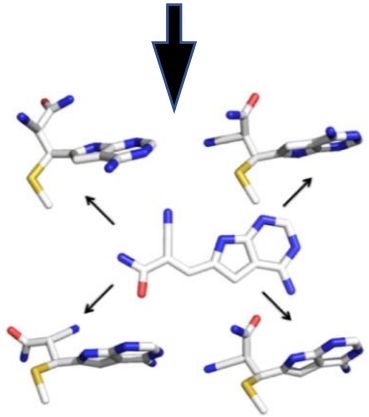
Proprietary chemical space of compounds

- D3 SPACE: 1.3M molecules with covalent warhead(s)
- CovDock by Schrödinger: Virtual Screening (VS) mode

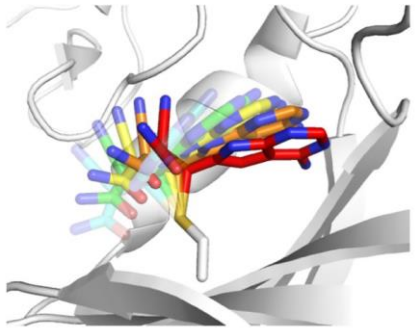




Curation of a virtual library of electrophiles.

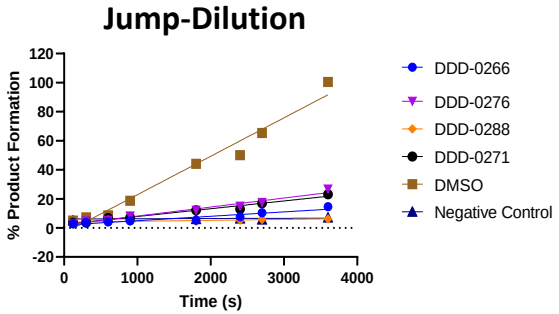


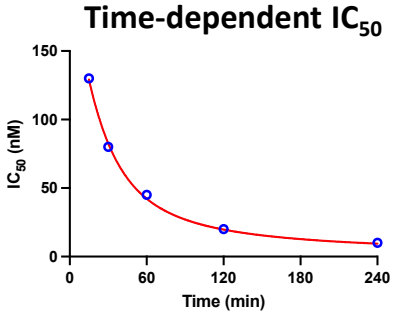
Generation of stereoisomers, ionization states and ligand conformations



Covalent docking: ligand sampling with covalent bond formation to a target residue

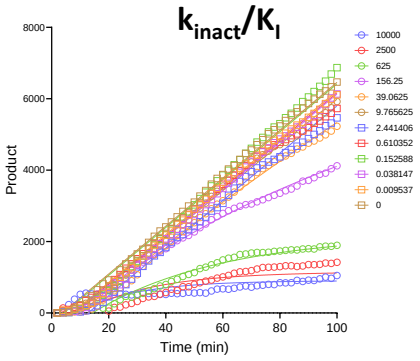
Biochemical: Time-dependent Covalent Engagement Characterization





- Time dependent product formation (activity) of enzyme after incubation with various inhibitors, followed by jump dilution

Time-dependent inhibition of Enzyme by a compound. IC_{50} values are shown to decrease as pre-incubation times increase.



- Assessment of a covalent modifier using a continuous enzyme assay enabling k_{inact}/K_I studies

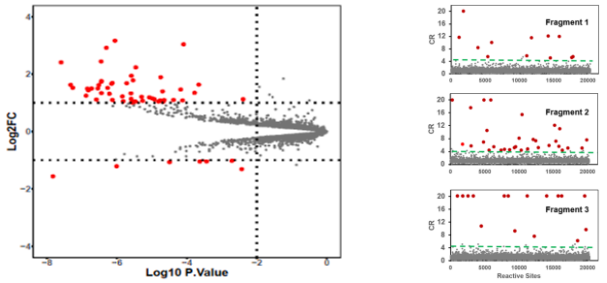
- **DSF experiments** to determine protein stability
- **DSLS experiments** to determine stability of proteins
- **ITD experiments** to determine Denaturation Rate and Half Life
- **ITC** to determine thermodynamics of binding
- **CD** to determine 2° structures of proteins
- **SPR** experiments to determine thermodynamics of binding

MS and (Chemo)Proteomics Capabilities:

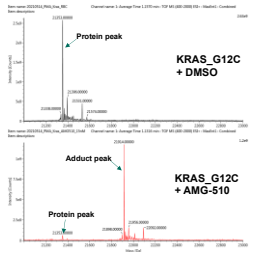
Proteomics Capabilities	Applications	TurnKey Advantage
Chemoproteomics	Target Site Identification, Selectivity Determination	Deep Profiling Of The Reactive Proteome (~20,000 Reactive Sites)
Whole-proteome Profiling	Mechanism Of Action Studies, Selectivity Determination	Deep Proteome Profiling (>5,000 Proteins) High Quantitative precision (CV < 4%)
Pulsed SILAC	Determination of protein homeostasis and turnover	High-throughput, high precision (Integration of SILAC with TMT technology)
Intact Mass Protein Analysis	Protein-compound Binding, Covalency Determination	Ultra-high Throughput Screening Capacity (>7000 Compounds/Week)
Peptide Mapping Analysis	Protein Sequencing, PTM Profiling, Binding Site Determination	High Sequence Coverage
Bioinformatics	Biostatistical Analysis, Network Enrichment, Hierarchical clustering	Comprehensive Data Analysis, Cloud-based/Interactive Data Visualization And Data Sharing

Chemoproteomics Discovery Platform

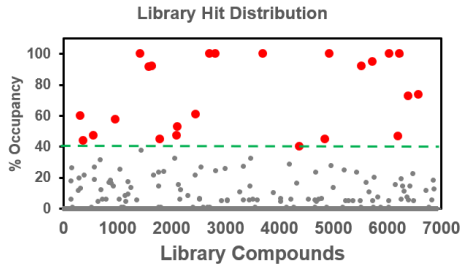
- **51,000** reactive protein sites mapped
- **>10,500** proteins with reactive sites mapped
- **>13,000 new** reactive sites identified
- **>440 new** proteins with reactive sites identified



Intact Mass Analysis Platform

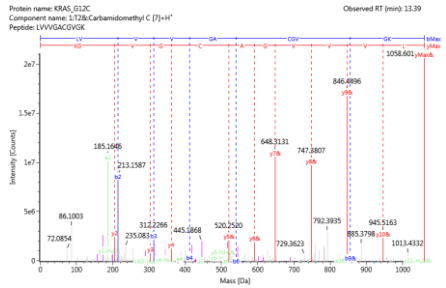


- Determination of %occupancy of AMG-510 on KRas G12C by IMA



- IMA screening of ~7,000 lead-like covalent molecules

Peptide Mapping Analysis



- Determining covalent binding site and characterization of recombinant protein sequence, isoforms, PTM, etc.
- A high-throughput covalent PMA platform enabled by plate-based sample processing, micro-flow chromatography, and the in-house PMA data analysis and QC tool.

Who We Are - Headquartered in Canada 🍁 Supporting Programs Globally

EXPERT & TOP QUALITY

Drug discovery expertise of world's top firms

Highly skilled scientists

State-of-the-art instrumentation

COST-EFFECTIVE

Highly competitive pricing enabled by our unique **Turn-Key Model**

Objective and milestone-oriented

THE

PREFERRED PARTNER FOR

DRIVING FAST-PACED INNOVATIVE PROGRAMS

IN SMALL MOLECULE DRUG DISCOVERY

AGILE AND RAPID EXECUTION

Fastest turn-around times

Full customization of R&D

Highest partner engagement

COMPREHENSIVE

The most comprehensive support from discovery to candidate nomination

Top partner support

Our Values

Accountable

Solutions Focused

Growth

Creative

What We Do

THE MOST COMPREHENSIVE SMALL MOLECULE DRUG DISCOVERY R&D SUPPORT

1

Evaluate

program science, IP & business objectives

2

Custom-build

internal R&D teams, program cascades & assays aligned with IP & business strategy

3

Efficiently execute

R&D across
Biology
Biochemistry
Proteomics
Chemistry
ADME
CADD

4

Manage

the entire or partial program including transparent outsourcing

5

Support

further technology development, IP & due diligence processes

The Turn-Key™ Model

From concept to PDC-ready

Unparalleled value-build and efficiency for any discovery program

Leading Bench-Side Expertise, Capabilities And Turn Around Times

A track-record for executing top-quality R&D for even the most complex programs at the bench-side

- Canadian team of **> 70% PhDs** across chemistry, CADD, *in vitro* biology, DMPK, and Proteomics
- 500+ publications; >300 years combined R&D experience
- Interdisciplinary teams **working side by side** for fully integrated programs
- Fastest turn around cycles
- State-of-the-art instrumentation and facilities

Strategic Guidance From Concept To PDC

Scientific oversight from industry experts to maximize program success

- Roster of experienced veterans and niche KOLS **>300 years** in pharma, biotech completed 100+ programs across various therapeutic areas and targets classes, and advanced multiple programs to DC, clinic and market
- Inventors on >150 patents; raised over $100 M, executed >$2 B in Pharma partnerships and founded multiple companies

Seamless Execution And Complete Integration

Dedicated, experienced program leaders and managers to deliver ultimate collaborative experience and rapid program progression

- Delivery of **consistent two-week design-make-test-analyze cycles**
- Selection and management of sub-contractors for niche needs and cost-effective solutions from an **expansive network** for complete integration.

Dalriada's IDD Leadership Experience and Philosophy

Dalriada's Discovery Strategy leadership team that will be assigned to your project have 140+ years integrated drug discovery (IDD) experience (in Pharma, CRO & Biotech) successfully leading small molecule projects through hit validation, H2L and LeadOp phases, identifying 41 Development Candidates.

- Project Led on 180+ IDD programs
- Delivering on challenging target classes including PPIs, Covalency, PROTACs and CNS
- Track record of delivering development-quality Candidates with clinical progress-ability; Over 20 molecules delivered to the clinic

Discovery lab teams are fully enabled to efficiently deliver IDD projects

Dalriada's shared IDD philosophy incorporates the following pillars to drive project outcomes

Rapid DMTA cycles

Co-localization, effective processes & monitoring – continuous improvement – maximizes learning iterations for the end-to-end R&D

Hypothesis driven design

Utilizing SBDD, CADD, pharmacophore, conformation and mechanism info – every compound counts and should address a question

Physiologically relevant endpoints & translation

Monitor formation of ternary complex & protein homeostasis, considering translation to patient group

Project back-planning

Visibility to # iterations and triggers for data collection, ensures **delivery focus on our shared goals** and value inflection points

Drug Discovery and R&D Leadership

Medicinal Chemistry


Jeff


Adam


Tom


Mark

Collectively: Over 275 years of drug discovery and specialty experience

Across 100+ different discovery programs & 6+ major therapy areas, including:

- Immuno-oncology
- Inflammation & Immunology
- Cardiovascular & Metabolic Diseases
- Neuroscience
- Oncology
- Anti-infectives

Biology/Pharmacology


Iain


Jeff


Diana

ADME / DMPK


Harpreet


Kevin

Biochemistry / Biophysics


Mohammad


Frosty

Proteomics


Uros


Taleb

Computational Chemistry


Andrew


Mike

Background:

charles river · DALTON Pharma Services · eurofins · illumina · CardinalHealth · NOVARTIS · Abbott · Lilly · Janpix · AstraZeneca · AMGEN · Boehringer Ingelheim · MERCK · evotec · OICR Ontario Institute for Cancer Research · ThermoFisher SCIENTIFIC · TRILLIUM · DUNAD · In4Derm Because Skin Matters · ALMAC · OTAVA chemicals · SGC · M4K PHARMA · TED ROGERS CENTRE FOR HEART RESEARCH

Learn More

For the full deck and case studies

Thank You!

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