A systems biology approach to elucidating and targeting tumor dependencies from patient-derived RNASeq profiles

A Foundational Initiative for precision-based compound pipeline optimization in oncology

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- DarwinHealth Inc.: Founder and Chair Scientific and Medical Advisory Board
- ThermoFisher Inc. SAB
- Cancer Genetics Inc. SAB
- DowAgrochemical: Consultant
Precision cancer medicine has been almost universally predicated on the ability to target oncogene mutations using targeted inhibitors (actionable mutations).

- **While There are Many Success Stories**
  - **BCR/ABL** Fusions: Imatinib
  - **HER2** Amplifications: Trastuzumab
  - **EGFR** Amplifications and activating mutations: Erlotinib, lapatinib, etc.
  - **ALK** mutations: Crizotinib
  - **BRAF V600E** mutations: Vemurafenib
  - ...

- **Serious Limitations and Barriers are Emerging**
  - Drugs targeting key oncogenes (e.g., PI3K, mTOR, AKT, MEK, ERK) have shown limited single-agent activity at tolerated doses [1].
  - Targeting most oncogenes (e.g., HER2, BRAF, EGFR, etc.) induces relapse to drug resistant tumors and poor prognosis [2].
  - High-affinity inhibitors for some key oncogenes (e.g., KRAS, MYC, etc.) are elusive.
  - We are running out of high penetrance alterations eliciting oncogene addiction
  - Some of the best drugs target key mechanisms rather than mutated proteins.
    - PDL1/CTLA-4, Glucocorticoids, Proteasome inhibitors, HDAC inhibitors, ...

2. Frank McCormick. *Cancer therapy based on oncogene addiction Journal of Surgical Oncology* 103, 6
Cancer and other diseases are the byproduct of aberrant protein activity.

Gene mutations are just one of many alternative ways to induce aberrant protein activity!
DarwinOncoTarget
Direct Assessment of Aberrant Protein Activity

- Optimized Protein-target based gene reporter assays
  - all COSMIC frequently altered oncogenes across >30 tumor types
  - ~2,000 Transcription Factors Proteins
  - ~4,000 Signal Transduction Proteins

- Full Regulatory Models for >30 Tumor types using ARACNe
  - TCGA
  - TARGET: Neuroblastoma
  - Other: GEP-NET, Lymphoma, AML, T-ALL, ...

- Meta-VIPER: Extension to rare or unprocessed tumor types

**Fundamental questions:**

- (a) Can one identify aberrantly activated oncoproteins (OncoTarget)?
- (b) What are the most differentially activated proteins (OncoTreat)?
Enrichment of specific gene point mutations in differential VIPER-inferred protein activity

Enrichment of overall gene-mutated samples in differential VIPER-inferred protein activity
All patients had activating EGFR mutations, including: 9 Exon 21 (L858R), 14 Exon 19 Del, 1 Exon 18 Mut., 3 Double Mut Classifier Trained on CCLE (Cell Line Data)

Major Collaborations with Strategic Research Centers to conduct large-scale retrospective and prospective clinical studies to validate DarwinHealth’s biomarkers.

Gustave Roussy, MD Anderson, Columbia/NYP

NY State CLIA Certified State with Columbia Pathology in the next 60-90 days

DarwinHealth’s biomarkers have an unprecedented potential to optimize and accelerate clinical studies

Collaboration with Naiyer Rizvi and Ramsey Asmards
Reproducibility of Differential Gene expression (RNASeq), Differential Protein Abundance (RPPA), and differential protein activity (VIPER/RNASeq):

Distribution of the top 10 genes or proteins in each of 190 triple negative TCGA BRCA samples, across the other 189 Samples.

Differential Gene Expression: Not Reproducible
Differential Protein Activity: Not Reproducible
Differential Protein Activity: Highly Reproducible

FFPE Analysis: Highly Reproducible
2M Read Indistinguishable from 30M Reads

FFPE reproducibility: Top 10 most differentially expressed genes and differentially active proteins in fresh-frozen vs. FFPE RNA-Seq

Activity inference highly reproducible when down-sampling RNA-Seq up to 500K reads
### Systematic Identification of actionable oncoproteins

- 5 – 20 actionable/patient

### High reproducibility

- Across multiple biopsies

### Longitudinal Tracking

- following progression
- following relapse
- following therapy

### Contextual and Global Evaluation

- Against similar tumors
- Against all of TCGA

### Supports Single Cell Analysis

- Assessing tumor Heterogeneity

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**Teniposide.** Type II topoisomerase inhibitor that causes dose-dependent single- and double-stranded breaks in DNA and DNA-protein cross-links.

**Etoposide.** Semisynthetic derivative of podophyllotoxin, which inhibits DNA synthesis via topoisomerase II inhibition activity.

**Daunorubicin.** Daunorubicin forms complexes with DNA by intercalation between base pairs, and it inhibits topoisomerase II activity by stabilizing the DNA-topoisomerase II complex, preventing the religation-recombination reaction that topoisomerase II catalyzes.

**Doxorubicin.** Antibiotic agent that inhibits DNA topoisomerase II and induces DNA damage and apoptosis.

**Mitoxantrone.** Type II topoisomerase inhibitor with IC_{50} of 2.6 μM, 0.42 mM for HepG2 and MCF-7/wt cells, respectively.

**Decitabine.** Inhibitor of DNA methylation with IC_{50} of 438 nM and 4.38 nM in HL-60 and KG1a cells, respectively.

**Belinostat.** HDAC inhibitor with IC_{50} of 27 nM, with activity demonstrated in cisplatin-resistant tumors. Phase 1/2.

**Panobinostat.** Broad-spectrum HDAC inhibitor with IC_{50} of 5 nM. Phase 3.

**Vorinostat.** HDAC inhibitor with IC_{50} of 10 nM.

**Trametinib.** MEK1/2 inhibitor with IC_{50} of 0.92 nM/1.8 nM, no inhibition of the kinase activities of c-Raf, B-Raf, ERK1/2. Phase 3.

**Palbociclib.** Palbociclib is an oral, reversible, selective, small-molecule inhibitor of CDK4 and CDK6, inducing arrest in G1-S phase.

**Epirubicin.** Semisynthetic L-arabino derivative of doxorubicin, is an antineoplastic agent by inhibiting Topoisomerase.
Systematic identification of candidate responder patients to targeted therapy across >30 cancers, using protein activity based biomarkers

Systematic identification of drug sensitivity biomarkers to rescue failed drugs, based on retrospective analysis of clinical trial FFPEs

Unprecedented level of reproducibility and applicability

DarwinHealth is the sole source for accessing proven technologies (**DarwinOncoTarget™**) to accomplish these commercial objectives in precision-focused cancer medicine.
Glioblastoma:
- Chen J et al. (2014) *Cell* 159(2).
  - Tumor Checkpoint: CEBP/D and Stat3
  - Alteration KLHL9

Diffuse Large B Cell Lymphoma:
  - Tumor Checkpoint: Nf-kB
  - Alterations: CARD11, A20, ...

GC-Resistance in T-ALL:
- Real PJ et al. (2013) *Cancer Cell* 24(6)
  - Tumor Checkpoint: NOTCH1/Akt1 pathways
  - Alterations: Pten, Pi3k

T-ALL Tumorigenesis:
- Della Gatta G et al. (2012) *Nature Medicine* 18(3)
  - Tumor Checkpoint: TLX1, TLX3, RUNX1
  - Alterations: TLX1, TLX3, RUNX1

Malignant Prostate Cancer:
  - Tumor Checkpoint: FOXM1 and CENPF

Trastuzumab Resistant HER2+/ER- Breast Cancer:
  - Tumor Checkpoint: pSTAT3

Follicular Lymphoma Progression to DLBCL:
  - Tumor Checkpoint: FOXM1, TFDP1, ATF5, HMGA1, NFYB

NBL, GEP-NET, LUAD, Infl. BRCA, Meningioma, OVCA, Pan-Cancer:
- In review or in submission
Cytokine loops promote breast cancer

Leslie K. Ferrarelli

The growth of some breast cancers is mediated by increased activity of the epidermal growth factor receptor HER2, but targeting HER2 directly has not been effective in halting tumor growth and progression. Rodriguez-Barrueco et al. found that the growth of HER2-positive tumors is driven by autocrine cytokine signaling that is targetable with FDA-approved drugs.

4 Patients enrolled so far (rapid untreatable progression)

One patient progressed:
- ER+: predicted!

Two patients had clinical response (One >17 weeks)
- ER- (predicted!): significant skin lesion improvement
- ER status unknown

One patient died of legionella (unrelated)
Analysis of 854 Prostate Cancer TMAs

Overall Survival 854 Patients TMA
- FOXM1+/CENPF+ p = 5.9 E-09
- FOXM1+/CENPF- p = 0.01
- FOXM1-/CENPF+ p = 0.4

28 Tumor Checkpoints Describe all of TCGA

Mesenchymal GBM

Proneural GBM

Luminal A

HER2+

Luminal A/B

Triple Neg.

01: BCL11B HOXA3 HOXA9 MYCN OLIG2
02: NFkB1 STAT3 SMAD9 CTNNB1 EP300
03: ZNF418 ZIK1 NXX2-1 ARNT TAL2
04: SMAD4 RBL1 ADNP SMAD2 VEZF1
05: PBX1 STAT5B MEIS3P1 ZNF620 ZNF793
06: DNM3A SOX4 E2F3 ILF3 TCF3
07: TFAP4 MESP1 PHF1 TRIM28 ZNF446
08: STAT5A IKZF1 TRIM22 KLF6 LMO1
09: TCF7L1 CUX1 THRA ZBTB18 FOXO4
10: WHSC1 E2F8 TP63 ATAD2 ELF4
11: MTA3 E2F6 BRD8 YY1 KCHN8
12: GAS7 SATB1 ZEB1 HEY2 FOXO1
13: ZNF782 ZBTB5 DZIP3 MLLT10 ZMYM2
14: TEAD3 CEBPB/D RELB NFkB2 OCT4
15: SCML2 ZNF3 SALL4 ZSCAN21 ONECUT2
16: ZEB2 NOTCH4 ERG FLI1 GATA1/2
17: AATF ZNF394 ZFYVE21 TSC22D4 TAF6
18: RUNX1 MMP14 WNT5A ETV5 ETV1
19: HOXA13 MSX1 HOXA11 TRIM16 SOX2
20: ZNF519 RCHY1 ZNF43 ZDHHC23 ZC3H8
21: BCL6 SMAD3 STAT6 RARA GLI3
22: TP53 DNM3B FOXM1 ETV4/6 CENPF
23: MYC HDAC1 TRIM27 CAMTA1 HMGA1
24: ESR1 PGR GATA3 NKX3-1 FOXA1
25: NOTCH1 RERE NOTCH3 BRPF1 ZHX3
26: GTF2IRD2B ZNF658 ZNF286B CTCFL ZNF578
27: MAX ZC3HC1 MSRB2 CERS4 DDIT3
28: ETS2 EPAS1 SOX7 SP6 BARX2 NR4A3
29: SOX9 SOX6 TCF7L2 BCL11A FOXC1
Tumor Checkpoints and Cancer Pathways

Hanahan, Weinberg, 2011
**Immune Checkpoint Inhibitors**

**Predicting Response**
Identifying MRs of Immune Checkpoint Inhibitor Activity

**Modulating Response**
(a) Abrogating activity of immunosuppressive TCs
(b) Targeting MRs of Resistance

**Complementing Response**
Targeting the vastly reduced sub-clonal representation following tumor checkpoint inhibitor therapy
Predicting Response to Immune Checkpoint Inhibitors

Can we identify (druggable) molecular markers associated to patient relapse following treatment with immune checkpoint blockade inhibitors?

Good prognosis: 7/9 responders (77%) vs. 9/17 (53%)
Poor prognosis: 15/19 relapsed (79%) vs. 7/8 (87%)
How Do We Match Drugs to Tumor Checkpoints?

- RNA-Seq Profiling in cell lines following perturbation with a library of ~2,000 small molecule compounds, including FDA approved and late stage experimental compounds. New PlateSeq Technology ($25/compound profile)
- VIPER\(^1\) identifies master regulators of compound activity, on a single sample basis
- SynGen\(^1,2\) identifies synergistic compound pairs, on a single sample basis
- DeMAND\(^3\) elucidates compound mechanism of action (>6 samples)

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DarwinOncoMatch™: Virtual Proteomics

- FOXM1 Tumor Signature
  - Underexpressed Genes
  - Overexpressed Genes

- Drug Perturbation Signature
  - IC20 48h
  - 1/10th IC20
  - 6h, 12h, 24h

- DarwinOncoMatch™: Virtual Proteomics
  - Drug A
  - FOXM1
  - Drug B
PLATESeq: Ultra-Efficient, Low-Cost, RNASeq

- Lyse cells in HTS plate
- Transfer to oligo(dT)-coated plate for mRNA capture
- Elute mRNA from oligo(dT)-coated plate
- Transfer to new plate for reverse transcription
- Add barcoded, adapter-linked oligo(dT) primers to each well
- Reverse Transcribe
- Pool barcoded cDNA

Remaining Steps Occur in a Single Sample

AUTOMATED

- Concentrate and purify with cDNA column
- Second-strand synthesis with adapter-linked random hexamers
- Purify ds-cDNA with Ampure beads
- PCR enrichment
- Purify Amplicons with Ampure beads
- Sequence to average depth of ~2 million reads/well
- Read 1: barcode
- Read 2: 3’-end of each gene

SINGLE POOLED SAMPLE

E. Gene Detection Saturation

F. MDS of Gene Expression

A. ERCC Counts vs Concentration
Inferring the Master Regulators of human disease (Disease MRs)

Tumor Checkpoint

Small Molecule Perturbations

Disease Initiation & Progression

Disease Signature

Regulatory Model

Inferring the Master Regulators of drug activity (Drug MRs)
Enrolling 260 patients in 14 rare or untreatable malignancies (>40 enrolled in 6 months):

- **14 Tumor types**: Glioblastoma, meningioma, neuroendocrine tumors, sarcoma, melanoma, pancreatic cancer, gastric cancer, breast cancer, H&N cancer, colon cancer, lung cancer, bladder cancer, ovarian cancer, prostate cancer.
- **5 arms open**: GBM, meningioma, breast cancer, GEP-NET, GIST sarcoma, pancreatic
- **Patient-derived Xenograft (PDX) models**: treated with MR-based drugs and drug combinations
- **Multiple funding sources**: NCI + philanthropy
- **Industrial Partners**: AstraZeneca, Novartis, Merrimack, Eli Lilly, Bayer

Completed/In Progress Drug Databases:

- Gastroenteropancreatic neuroendocrine tumors (GEP-NET)
- Triple Negative Breast Adenocarcinoma,
- GIST sarcoma
- Anaplastic meningioma
- Glioblastoma
- In progress (funded): Bladder, Lung, Pancreatic, Neuroblastoma (pediatric),

Fundraising/Planning Stage ($5M)

- Colon, gastric, melanoma, small cell lung, H&N, ovarian, prostate
### Comparative Analysis of NET Met MRs

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**CTLA-4 Ligand/Modulator**

- Experimentally validated by shRNA mediated silencing
Drugs with $p < 1E-10$ achieve excellent reversal of MR signature.

$HC = 48h IC_{20}$; $LC = 1/10^{th} 48h IC_{20}$
In Vivo Validation: H-STS Xenograft

Differential compound activity *in vitro* (H-STS and KR1J vs. 400 CCLE lines) did not correlate with MR-predicted and experimentally validated *in vivo* activity.
Metastatic KRAS$^{\text{Mut}}$/SDHB$^{\text{Del}}$ GIST Sarcoma

**Selumetinib**

- **Vehicle**
- **Selumetinib**

$n=3$
$p=0.0445$

**Teniposide**

- **Vehicle**
- **Teniposide**

$n=2$

**Topotecan**

- **Vehicle**
- **Topotecan**

$n=3$
$p=0.0245$

**Danunorubicin**

- **Vehicle**
- **Daunorubicin**

$n=3$
$p=0.1253$

**Fludarabine**

- **Vehicle**
- **Fludarabine**

$n=2$

**Chloropromazine**

- **Vehicle**
- **Chloropromazine**

$n=3$
$p=0.7027$
Option 1: Design of Novel Clinical Studies (Prospective and Retrospective)

- Elucidation of RNA/Protein-activity based Response Biomarkers
  - Targeted therapy and Immunotherapy
- Elucidation of Sensitizers compounds to rescue compound sensitivity
  - Targeted + targeted
  - Immune + targeted
- Design of Meta-genomic Basket Studies
- Time Requirements:
  - Ultra-efficient: < 1 week with ongoing data collection, allowing efficient adaptive basket study design

Option 2: Characterization of Proprietary Compound Libraries: 1 – 1,000 compounds

- MoA: Unbiased, genome-wide characterization of compound MoA in >80% of tumor contexts
- Therapeutic Value Assessment of compounds across >80% of tumor contexts
  - Conventional: Targeted oncprotein inhibitors
  - Immuno-oncology: Immune checkpoint inhibitors
  - Unconventional: Tumor-checkpoint inhibitors
- Combination Therapy: Assessment of compound synergy across >80% of tumor contexts
- Drug Sensitivity and Drug PD Biomarkers:
  - Responders: Assessment of biomarkers of compound sensitivity
  - PD: Assessment of biomarkers of compound response
- Time Requirements:
  - 6 – 18 months
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