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Bethesda, Maryland
Precision therapeutics can be defined as the ability to:

• prescribe effective therapies only to those patients who will respond effectively (cure),
• while limiting toxicity to normal tissues and minimizing side effects.
Synthetic lethality beyond BRCA and PARP inhibitors
  - TOP1 inhibitors

Cancer Cell Line genomics as model systems

SLFN11 as a highly penetrant determinant of response

Practical implications: example of temozolomide
Synthetic lethality beyond BRCA and PARP inhibitors
- TOP1 inhibitors

- Cancer Cell Line genomics as model systems
- SLFN11 as a highly penetrant determinant of response
- Practical implications: example of temozolomide
Synthetic lethality for BRCA cells beyond PARP inhibitors

TOP1 inhibitors

DT40 cells

DLD1 cells
Camptothecin derivatives (Irinotecan and Topotecan) are potent anticancer agents and highly selective TOP1 inhibitors.

Camptothecins are selective for HR (BRCA) deficient tumors.

Camptothecins are the only chemical class of TOP1 inhibitors (many tubulin, TOP2...).

Camptothecins have well-established limitations:

- Chemically unstable (inactivated within minutes in plasma)
- Reversibly block TOP1-DNA complexes (long exposure required to maximize effect)
- Eliminated from cancer cells by ABC drug efflux transporters (ABCG2 – ABCB1)
- Short plasma half-life (2-3 hours due to rapid clearance)
- Dose-limiting bone marrow toxicity
- Severe diarrhea (Irinotecan)
Non-camptothecin TOP1 inhibitors developed by the NCI: the **Indenoisoquinolines**: the LMPs

**LMP400** (Indotecan) and **LMP776** (Imidotecan) completed Phase 1  
**LMP744** is beginning phase 1
Synthetic lethality of the indenoisoquinolines for BRCA cells beyond PARP inhibitors

Indenoisoquinoline TOP1 inhibitors are potent as single agents at nanomolar concentration in HR deficient cells

Indenoisoquinolines synergize with olaparib in BRCA1-deficient cells
The indenoisoquinoline TOP1 inhibitors are in Phase 1-2 clinical development

- As the TOP1 inhibitor camptothecin derivatives (Irinotecan and Topotecan), the indenoisoquinolines are potent anticancer agents
- Camptothecins are the only chemical class of TOP1 inhibitors (many tubulin, TOP2...)
- The indenoisoquinolines are selective for HR (BRCA) deficient tumors
- The Indenoisoquinolines overcome the limitations of camptothecins
  - Chemically unstable (no lactone E-ring)
  - More stable block of TOP1-DNA complexes than camptothecins
  - Eliminated from cancer cells by ABC drug efflux transporters (ABCG2—ABCB1)
  - Short Long plasma half-lifes (12-17 hours vs. 2 hours)
  - Dose-limiting bone marrow toxicity
  - Severe diarrhea (Irinotecan)
Synthetic lethality beyond BRCA and PARP inhibitors
- TOP1 inhibitors

Cancer Cell Line genomics as model systems

- SLFN11 as a highly penetrant determinant of response
- Practical implications: example of temozolomide
Our mission is to integrate pharmacological, genomics, proteomic and metadata to:
1. Discover new drug response determinants (sensitivity <-> resistance; signatures)
2. Enable others to make new discoveries through user friendly interface across multiple cancer cell lines databases

CellMiner is a unique facility open world wide with over thousands of user monthly since its inception.
It can be accessed through:  
http://discover.nci.nih.gov/cellminer  
http://discover.nci.nih.gov/cellminercdb
The publicly available cancer cell line databases and the CellMiner website

Developmental Therapeutics Program
NCI/NIH

http://discover.nci.nih.gov/cellminer/
http://discover.nci.nih.gov/cellminercdb/

GDSC (CGP)

http://www.cancerrxgene.org/ (Genomics of Drug Sensitivity in Cancer Project)

CCLE

http://www.broadinstitute.org/ccle/ (Broad-Novartis Cancer Cell Line Encyclopedia)

CTRP

http://www.broadinstitute.org/ctrp/ (Stuart L. Schreiber Research Laboratory)
CellMiner CDB (Cross Data Base): a new online tool for the community of biomedical researchers, biologists and pharmacologists

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~ 80,000 genomic parameters

**CELL LINES**

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**DRUGS**

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http://discover.nci.nih.gov/cellminercdb
Goal: Discovering clinically-relevant cancer biology and identifying molecular determinants of cancer drug responses

Cell Line Data Sources
- NCI (NCI-60, SCLC)
- MGH/Sanger (GDSC)
- Broad (CCLE, CTRP)

Website Features
- Assessment of Data Reproducibility
- Multivariate Models of Drug Response & Genomic Features
- Bivariate Analysis for Any Data Features
- Tissue-type Restricted Analyses
- Pathway Annotated Results
- Drug Identifier Conversion

Available Data
- Mutation
- Protein Levels
- Methylation
- Dose Response
- Transcriptomics
- Copy Number
- MicroRNA

http://discover.nci.nih.gov/cellminercdb/
CellMiner CDB: the power of Cross DataBase analyses (SLFN11 as test run)
Reproducibility is high across databases (cell lines are comparable at the genomic level)

http://discover.nci.nih.gov/cellminercdb

Deletion

0
Anticancer sulfonamides target splicing by inducing RBM39 degradation, via recruitment to DCAF15

Ting Han, Maria Gorshkova,* Nicholas Gaskill,* Emanuela Capota, Jiwoong Kim, Tabitha C. Ting, Yang Xie, Noodle S. Williams, Deepak Nijhawan*

INTRODUCTION: Indolium is an aryl sulfonamide drug that inhibits the proliferation of certain human cancer cell lines. Its mechanism of action and the mechanism underlying its selectivity are poorly understood. On the basis of its anticancer activity in vitro and in mice, indolium has been extensively tested in patients with advanced-stage solid tumor. No unacceptable toxicities were reported in patients receiving indolium monotherapy, but fewer than 10% of patients showed a clinical response.

RATIONALE: At present, there is no way to predict which cancer patients are most likely to benefit from indolium treatment. We reasoned that a better understanding of the molecular mechanism underlying indolium’s anticancer activity might reveal why only a subset of tumors respond to it. This in turn might lead to more effective clinical use of the drug. To study indolium’s mechanism of action, we identified genetic mutations that confer resistance to its cytotoxic effect.

RESULTS: Using a forward genetic strategy, we discovered that several single amino acid substitutions in a nuclear protein called RBM39 (RNA binding motif protein 39) confered resistance to the toxic effects of indolium in cultured cancer cells and in mice with tumor xenografts. In the presence of indolium, RBM39 associated with the CUL4-DDB1-DDA1-DCAF15 E3 ubiquitin ligase complex (CUL4-DCAF15), leading to polyubiquitination and proteasomal degradation of RBM39. Mutations in RBM39 led to aberrant pre-mRNA splicing, including intron retention and exon skipping, in hundreds of genes.

In a large survey of indolium sensitivity across more than 800 cancer cell lines, we found that cancer cells derived from the hematopoietic and lymphoid (HL) lineages were more sensitive to indolium than cancer cells derived from other lineages. In HL cancer cell lines, DCFS mRNA expression levels and DCAF15 gene copy number variation directly correlated with indolium sensitivity.

CONCLUSION: Cancer genome–sequencing studies have highlighted the importance of pre-mRNA splicing in tumorigenesis. Drugs such as indolium, taisulam, and CQS—which we collectively refer to as SPLAMs (splicing inhibitor sulfonamides)—provide a strategy to target RBM39-dependent pre-mRNA splicing in cancer. Many of the earlier clinical trials of indolium focused on patients with solid tumors. Our findings suggest that indolium may be most effective in patients with leukemias and lymphomas that express relatively high levels of DCAF15.

The activity of SPLAMs resembles that of IMiDs (immunomodulatory drugs). IMiDs are selective for either species alone. RBM39 mutations that cause indolium resistance impeded the formation of this complex. Interestingly, we found that two other clinically tested sulfonamides with structural similarity to indolium—taisulam and chloroquinoxaline sulfonamide (CQS)—share the same mechanism of action as indolium. RBM39 is a nuclear protein that is involved in precursor mRNA (pre-mRNA) splicing. Biochemical isolation of RBM39 revealed an association with numerous splicing factors and RNA binding proteins. We found that degradation of RBM39 by indolium led to aberrant pre-mRNA splicing, including intron retention and exon skipping, in hundreds of genes.

For full article visit: http://science.sciencemag.org/content/356/6337/397

http://discover.nci.nih.gov/cellminer/cdb

Blood and Lymph cell lines colored in red

Validation of Exceptional Responders in Cancer Cell Lines (CTRP-CCLE cancer cell line encyclopedia (Stuart Schreiber))
Other synthetic lethal interactions and genomic signatures to determine rational indications and combinations

CellMiner CDB ([http://discover.nci.nih.gov/cellminercdb](http://discover.nci.nih.gov/cellminercdb))

Univariate Analysis

Regression Analysis - Multivariate Analysis - Lasso Regression Analyses

100 most sensitive (green) and most resistant (red) cell lines are displayed above

(see CellMiner website)
Synthetic lethality beyond BRCA and PARP inhibitors

- TOP1 inhibitors

Cancer Cell Line genomics as model systems

SLFN11 as a highly penetrant determinant of response

Practical implications: example of temozolomide
The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity

Jordi Barretina1,2,3,*, Giordano Caponigro4, Nicolas Stransky4, Kavitha Venkatesan4, Adam A. Michael A. Shyr4, Christopher J. Wilson4, Joseph Lehár4, Gregory V. Kryukov4, Dmitry Sonkin4, Anupama Reddy4, Abhishek Mahajan4, Michael F. Berger4, John E. Monahan4, Paula Morais4, Jodi Meltzer4, Adam Korejwa1, Judit Jané-Val1, Joseph Thibault4, Eva Bric-Furlong4, Pichai Raman2, Aaron Shipway2, Ingo H. Engels2, Jill Cheng6, Peter Aspesi Jr6, Melanie de Silva5, Kalpana Jagtap5, Michael D. Jones6, Li Wang6, Charles Hatton2, Supriya Gupta1, Scott Mahan1, Carrie Sougnez1, Robert C. Onotiro1, Ted Liefield2, Laura MacConaill1, Michael Reich1, Namxin Li2, Jill P. Mestrov2, Stacey B. Gabriël2, Gad Getz3, Kristin Ardile2, Vivien Cha6, Barbara L. Weber6, Jeff Porter6, Markus Warmuth6, Peter Finan6, Jennifer L. Harris2, Matthew Meyer2, Anupama Reddy4, Michael P. Morrissey4, William R. Sellers4, Robert Schlegel3, and Levi A. Garraway1,2,3

The systematic translation of cancer genomic data into knowledge of tumour biology and therapeutic possibilities remains challenging. Such efforts should be greatly aided by robust preclinical model systems that reflect the genomic diversity of human cancers and for which detailed genetic and pharmacological annotation is available. Here we describe the Cancer Cell Line Encyclopedia (CCLE): a compilation of gene expression, chromosomal copy number and massively parallel sequencing data from 947 human cancer cell lines. When coupled with pharmacological profiles for 24 anticancer drugs across 479 of the cell lines, this collection allowed identification of genetic, lineage, and gene-expression-based predictors of drug sensitivity. In addition to known predictors, we found that plasma cell lineage correlated with sensitivity to IGF1 receptor inhibitors; AHR expression was associated with MEK inhibitor efficacy in NRAS-mutant lines; and SLFN11 expression predicted sensitivity to topoisomerase inhibitors. Together, our results indicate that large, annotated cell-line collections may help to enable preclinical stratification schemata for anticancer agents. The generation of genetic predictions of drug response in the preclinical setting and their incorporation into cancer clinical trial design could speed the emergence of ‘personalized’ therapeutic regimens.

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1Laboratory of Molecular Pharmacology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892; 2Department of Internal Medicine, University of Nevada and Institute of Ricerco a Gura a Carattere Scientifico Azienda Ospedaliera Universitaria San Martino, Instituto Nazionale per la Ricerca sul Cancro, 16132 Genoa, Italy; and 3Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892

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Present addresses: Novartis Institutes for Biomedical Research, Emeryville, California 94608, USA.

Published October 23, 2012

Published online September 20, 2012

To whom correspondence should be addressed.
Determinants of response to PARP inhibitors beyond BRCA and MDR

Panel of DT40 Single Knockouts (Shunichi Takeda)


PARP inhibitor = DNA Repair Inhibitor

PARP inhibitor = DNA Damaging Agent
Clinical PARP Inhibitors that trap PARP have most extended and rigid chemical structures

- **Veliparib ABT-888**: Least Trapping, Good catalytic inhibition
- **Niraparib MK-4827**: Least Trapping
- **Talazoparib BMN-673**: Most trapping
- **Rucaparib AG-014699**: Most trapping
- **Rubraca FDA Approved Dec 2016**
- **Zejula FDA Approved March 2017**
- **Olaparib: Lynparza AZD-2281**: FDA Approved Dec 2014

*Pommier, O’Connor, de Bono 2016 Science TM*
BRCA-independent determinant of talazoparib sensitivity

Sixty cancer cell lines

Sensitive to talazoparib

Resistant to talazoparib

Homozygous mutation of BRCA1: 0/60
Homozygous mutation of BRCA2: 1/60
(Sousa et al., DNA repair, 2015)

NCI-60

Very potent

C_{max}: 50 nM

Developmental Therapeutic Program

IC_{50} for Talazoparib (=BMN674) (µM)

=> CellMiner (cdb) COMPARE analysis
Sanger database
1000 cancer cell lines

PARP inhibitor
Talazoparib

Drug discovery signatures
http://discover.nci.nih.gov/cellminercdb
High correlation between expression of *Schlafen 11* (*SLFN11*) and cellular response to talazoparib

\[ r = 0.612, \ p < 10^{-7} \]

CellMiner
http://discover.nci.nih.gov/

Developmental Therapeutic Program
High correlation between expression of *Schlafen 11* (SLFN11) and cellular response to talazoparib

\[ r = 0.612, \ p < 10^{-7} \]

CellMiner

http://discover.nci.nih.gov/
Molecular biology: SLFN11

- A member of the Schlafen (SLFN) family, found only in mammals;
- Located in the nucleus;
- A putative DNA/RNA helicase;
- Binds to chromatin, RPA at damage sites, tRNA…
- Transcriptionally regulated by:
  - *ETS transcription factors* (*EWS-FLI1 in Ewing's*)
    (*Clin Cancer Res 2015*)
  - *Promoter methylation*
    (*Oncotarget 2015; Cancer Res 2017*)
- Determines sensitivity to *PARP inhibitors* (*Oncocotarget 2016*)

Schlafen = To sleep in German
SLFN11 inactivation in 4 different isogenic cell lines confers high resistance to PARP inhibitors

=> SLFN11 inactivation is a novel mechanism of resistance to PARP inhibitors

DU145: Prostate cancer
MOLT4 and CCRF-CEM: Leukemia
EW8: Ewing’s sarcoma
(CRISPR/Cas9)

SLFN11 determines response to a broad range of DNA-targeted agents: TOP1, TOP2, PARP inhibitors, cisplatin, carboplatin, gemcitabine, hydroxyurea...
SLFN11 induces lethal replication arrest independently of ATR and BRCA1/2
In the absence of SLFN11 (≈ 50% cancer cell lines: HeLa, U2OS, HCT116, RKO, MCF7, MDA-MB231...), ATR-CHK1 transiently arrests replication to allow DNA repair.

**SLFN11** binds to stressed replication forks through RPA, and arrests replication by blocking the replicative helicase complex.
SLFN11 is inactivated in ≈ 45% of cancer cell lines

Especially in the cancer cell lines that are commonly used for screening resistance to PARP inhibitors

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<th>Dataset</th>
<th>SLFN11 mRNA (Log2)</th>
<th>Expression Rate</th>
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<td>CCLE</td>
<td>43% (440/1036)</td>
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<tr>
<td>GDSC</td>
<td>52% (528/1013)</td>
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</table>
Broad range of SLFN11 expression in tumor tissue

SLFN11 mRNA expression (RNA-Seq)

The Cancer Genome Atlas (TCGA)
The regulation of SLFN11 in cancers:

- Transcriptional target of FLI1 and ETS (Ewing’s) (Tang, S. 2015)
- Inactivation in about 40% of cancer cell lines (NCI-60 and CCLE) (not by gene deletion)
SLFN11 inactivation in about 40% of cancer cell lines is in part due to epigenetic imprinting by promoter methylation.
SLFN11 inactivation in about 40% of cancer cell lines is in part due to epigenetic imprinting by promoter methylation.

CCLE and GDSC Cross database Analysis with Cellminer cdb
SLFN11 inactivation by promoter methylation correlates with resistance to a broad range of DNA damaging agents (NCI-60 database)

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Reinhold, W....Doroshow, J...Pommier 2017 Cancer Res
Synthetic lethality beyond BRCA and PARP inhibitors
  TOP1 inhibitors
Cancer Cell Line genomics as model systems
SLFN11 as a highly penetrant determinant of response
Practical implications: example of temozolomide
Temozolomide (TMZ) is an oral DNA methylating prodrug approved for glioblastomas based on:

- its selective cytotoxicity in methylguanine methyltransferase (MGMT)-deficient cells (which is frequent in glioblastomas)
- its liposolubility and blood-brain barrier (CNS) penetration.
- its relatively low cytotoxicity to normal cells (dose limiting toxicity: bone marrow)
In normal cells TMZ tends to be non-cytotoxic
In MGMT-deficient cells TMZ is cytotoxic by MMR.
Both MGMT and MMR determine resistance to temozolomide
MGMT determination and staging based on cancer cell lines (NCI-60)

- MGMT deficiency is frequent (1/3 of NCI-60) and not limited to CNS cancer cells.
- High correlation between protein expression (measured by RPPA – reverse phase protein array - Gordon Mills) => transcripts or protein are reliable.
- Poorer performance for promoter methylation ⇔ methylation misses many cell lines such as the CNS, which have no protein (and transcript).
Bladder Urothelial Carcinoma
Breast Invasive Carcinoma
Cervical Tumor (SCC and EA)
Colon Adenocarcinoma
Head and Neck Tumor (SCC)
Kidney Chromophobe Normal
Kidney Chromophobe Tumor
Renal Clear Cell Carcinoma Normal
Renal Clear Cell Carcinoma Tumor
Renal Papillary Cell Carcinoma Normal
Renal Papillary Cell Carcinoma Tumor
Liver Hepatocellular Carcinoma
Lung Adenocarcinoma Normal
Lung Adenocarcinoma Tumor
Lung Squamous Cell Carcinoma Normal
Lung Squamous Cell Carcinoma Tumor
Pancreatic Adenocarcinoma
Prostate Adenocarcinoma
Rectum Adenocarcinoma
Sarcoma Normal
Sarcoma
Thyroid Carcinoma
Uterine Corpus Endometrial Carcinoma Normal
Uterine Corpus Endometrial Carcinoma
Glioblastoma Multiforme
Acute Myeloid Leukemia
Brain Lower Grade Glioma
Ovarian Serous Cystadenocarcinoma
Uterine Carcinosarcoma

MGMT expression TCGA
mRNA expression (RNA-seq)

Low MGMT
High MGMT
MGMT is a gene whose epigenetic silencing by DNA methylation level is a positive prognostic indicator for temozolomide treatment (41). In the NCI-60, DNA promoter methylation levels above 40% appear to affect MGMT expression levels, but result in background levels for only a portion (81.2%) of those cell lines. In addition, DNA promoter methylation levels less than 40% occur in only a portion (81.8%) of expressed cell lines. Thus MGMT methylation is a useful but incomplete indicator of MGMT expression, and for the cell lines is as predictive for all other tissue of origin types (excepting colon with two out of seven expressed in the presence of >40% methylation) as it is for the glioblastomas (CNS).

MGMT promoter methylation is not a “precise” measure of MGMT status (transcripts or protein).
MGMT promoter methylation is not a “precise” measure of MGMT status (transcripts or protein).
High correlation between transcripts and protein for MGMT across the NCI-60

Synthetic lethality beyond BRCA and PARP inhibitors
- TOP1 inhibitors

Cancer Cell Line genomics as model systems

SLFN11 as a highly penetrant determinant of response

Practical implications: example of temozolomide

DNA repair alterations are frequent in cancers
### Testable genomic signatures

#### Matching DNA targeted drugs and genes

<table>
<thead>
<tr>
<th>Drugs</th>
<th>SLFN11</th>
<th>ABCG2</th>
<th>ABCC3</th>
<th>ABCB1</th>
<th>LMNA</th>
<th>TOP1</th>
<th>TOP2A</th>
<th>MGMT</th>
<th>MMR</th>
<th>MYC</th>
<th>MYCL</th>
<th>MYCN</th>
<th>TP53 (mut)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOP1 inhibitors (camptothecins, indenos)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>0</td>
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<tr>
<td>TOP2 (Daunorubicin, Etoposide)</td>
<td>1</td>
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<td>?</td>
<td>1</td>
<td>?</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>0</td>
</tr>
<tr>
<td>PARP inhibitors (olaparib, talazoparib, niraparib)</td>
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<td>0</td>
<td>?</td>
<td>1</td>
<td>?</td>
<td>0</td>
<td>0</td>
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<td>?</td>
<td>?</td>
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<tr>
<td>Temozolomide</td>
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<td>?</td>
<td>?</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>1</td>
</tr>
<tr>
<td>ATR inhibitors (VE-970; AZD6738)</td>
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<td>?</td>
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<td>?</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Wee1 inhibitor (AZD1775)</td>
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<td>?</td>
<td>?</td>
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<td>?</td>
<td>?</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Chk1/2 inhibitor (LY-2606368; Prexasertib)</td>
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<td>?</td>
<td>?</td>
<td>0</td>
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<td>1</td>
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</tbody>
</table>

### Genomic Biomarkers

- **SLFN11** exp
- **ABCG2** exp
- **ABCC3** exp
- **ABCB1** exp
- **LMNA** exp/mut
- **TOP1** exp
- **MGMT** exp
- **MMR** (MLH1, MLH3, MSH2, MSH3, MSH6, PMS1 and PMS2) exp/mut
- **MYC** exp
- **MYCL** exp
- **MYCN** exp
- **TP53** mut
Synthetic lethality beyond BRCA and PARP inhibitors
  ➢ TOP1 inhibitors
Cancer Cell Line genomics as model systems
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Precision therapeutics can be defined as the ability to:
• prescribe effective therapies only to those patients who will respond effectively (cure),
• while limiting toxicity to normal tissues and minimizing side effects.
### Second Generation Camptothecins with Targeted Delivery

<table>
<thead>
<tr>
<th>Name</th>
<th>Company</th>
<th>Active Derivative (Payload)</th>
<th>Formulation (Conjugate; Target)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onivyde™ = MM398*</td>
<td>Merrimack</td>
<td>Irinotecan</td>
<td>Liposome</td>
</tr>
<tr>
<td>CRLX101</td>
<td>Cerulean Pharma Inc.</td>
<td>Camptothecin</td>
<td>PEG</td>
</tr>
<tr>
<td>NKTR-102</td>
<td>Nektar Therapeutics</td>
<td>Etirinotecan (20 position)</td>
<td>PEG (Pegol)</td>
</tr>
<tr>
<td>PLX038</td>
<td>ProLynx</td>
<td>SN-38</td>
<td>PEG</td>
</tr>
<tr>
<td>IMMU-132 = Sacituzumab govitecan **</td>
<td>Immunomedics (Seattle Genetics)</td>
<td>SN-38 (20 position)</td>
<td>ADC - TROP2 (TACSD2)</td>
</tr>
<tr>
<td>IMMU-130 = Labetuzumab govitecan **</td>
<td>Immunomedics</td>
<td>SN-38</td>
<td>ADC-CEACAM5</td>
</tr>
<tr>
<td>DS-8201a ***</td>
<td>Daichi Sankyo</td>
<td>DXd (Exatecan)</td>
<td>ADC – HER2</td>
</tr>
<tr>
<td>PEN-866</td>
<td>Tarveda Therapeutics</td>
<td>SN-38 (10 position)</td>
<td>Conjugate Hsp90</td>
</tr>
<tr>
<td>NK012</td>
<td>Nippon Kayaku</td>
<td>SN-38</td>
<td>Polymeric micelles (PEG-polyglutamate)</td>
</tr>
<tr>
<td>ALOS4-CPT</td>
<td>Ariel University</td>
<td>Camptothecin</td>
<td>HDC – ALOS-4</td>
</tr>
</tbody>
</table>

* FDA Approved, October 2015
** FDA Breakthrough, February 2016
*** FDA Breakthrough, August 2017 (Breast)
Acknowledgements (present lab members):

Junko Murai
PARPi
SLFN11
HR TOP1

Vinodh Rapajakse
CellMiner

Margot Sunshine

Bill Reinhold

http://discover.nci.nih.gov/cellminer
http://discover.nci.nih.gov/cellminercdb

Augustin Luna

James Doroshow
PARPi
TOP1 inhibitors clinical trials
NCI-60