NEW DEVELOPMENTS IN EPIGENETICS AND POTENTIAL CLINICAL APPLICATIONS

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Targeting the Epigenome

Meaning that we identify proteins that impact transcriptional controls that are important in cancer.

Epigenetics – Meaning the right genes expressed at the right time, in the right place and in the right quantities. This process is ensured by an expanding list of genes that themselves must be expressed at the right time and right place.

Think of it as a coordinated chromatin dance involving DNA, histone proteins, transcription factors, and over 700 proteins that modify them.
Transcriptional Control:

DNA Methylation
Histone Tail Modification
Nucleosomal Remodeling
Non-Coding RNA
HISTONE PROTEIN FAMILY

- 146 bp DNA wrap around an octomer of histone proteins
- H2A, H2B, H3, H4 are core histone families
- H1/H5 are linker histones
- >50 variants of the core histones
- Some with unique functions
- Post translational modification of “histone tails” key to gene expression
- Post-translational modifications include:
  - Acetylation
  - Methylation
  - Ubiquitination
  - Phosphorylation
  - Citrullation
  - SUMOylation
  - ADP-ribosylation
Specific histone modifications determine function

- H3K9Ac, H3K27Ac, H3K36Ac
- H3K4Me3 – Gene activation
- H3K36Me2 – Inappropriate gene activation
- H3K27Me3 – Gene repression; Inappropriate gene repression
- H2AX S139Phosphorylation – associated with DNA double strand break, repair

http://www.slideshare.net/jhowlin/eukaryotic-gene-regulation-part-ii-2013
**KEY MODIFICATION - SPECIFIC FUNCTIONS**

- **H3K4Me**: Key Activating Residue
- **H3K4Ac**: Activating Residue
- **H3K9Ac**: Activating Residue
- **H3K27Me**: Key Silencing Residue
- **H3K36Me**: Active transcription, RNA elongation
- **H4K20**: DNA damage

**Activation**

**Promoter or activation**

**Heterochromatin or repression**

**Elongation**

**Enhancer**

**DNA damage**

At least 700 proteins are thought to be involved in regulating/reading these post translational modifications. Many of these have been discovered to bear mutations in cancer and many are considered targets for drug development.

CRITICAL EPIGENETIC REGULATORS CLASSIFIED

Writers
- Acetylases
- Methylases
- Phosphorylases

Erasers
- Deacetylases
- Demethylases
- Phosphatases

Readers
- Bromodomain
- Chromodomain
- Proteins

Movers
- Chromatin Remodelers

Shapers
- Histone Proteins

565 genes that affect histone modifications

108 genes that affect chromatin remodeling “movers”

36 genes that affect DNA methylation

From the International Cancer Genome Consortium: Often mutated

CRITICAL EPIGENETIC REGULATORS

Are often altered or mutated in cancer and thus targets for therapy

Acetylases, Methylases, phosphorylases
- DNMT1
- DNMT 3A/B
- EZH2
- SETD2
- MLL
- NSD2

Deacetylases, demethylases, phosphatases
- KDM6A (UTX)
- TET2
- IDH1/2
- HDAC
- KDM1A (LSD1)

Bromodomain, chromodomain, proteins
- BRD4

Remodelers
- SWI/SNF
- SMARC
- ARID
- ISWI
- CHD
- INO80

Histones
- HIST1H1B
- HIST1H1C
- HIST1H3B
- H3F3A

Aberrant DNA methylation in cancer:
- Methylation of cytosines in CPG islands
- Methylation of CPG shores
- Demethylation of gene bodies
- Demethylation of repetitive elements

Mutations in DNMT, TET2, IDH2 all associated with abnormal DNA methylation

Mutation is associated with repression of genes controlling differentiation

EPIGENETIC REGULATORS

DNA methylation as a target for drug development

DNA methyltransferases (DNMT 1, 3A, 3B) often mutated in cancer
DNMT inhibitors **5-Azacytidine and Decitabine**
FDA approved in myelodysplastic syndrome (MDS)
Responses in about 15% of patients with MDS
DNMT mutated in 22% of acute myelogenous leukaemia
  - Founder mutation: occurs in pre-leukemic clones, frank leukaemia occurs when oncogenic drivers emerge
  - Persists through treatment and relapse
Mutated in 33% of AILT subtype of peripheral T-cell lymphomas
Mutations in TET2 and IDH1 and 2 also promote methylation
STUDIES OF CLONAL ARCHITECTURE

In acute leukaemia show DNMT3A mutation from earliest precursor

1. DNMT3A, NPM1
2. FLT3/IDH1
3. IDH2/RUNX1
4. FOXP1/FLT3
5. CXCL17
6. UNKNOWN DRIVER
7. TP53/KCNT1
PERIPHERAL T-CELL LYMPHOMA

Three distinct routes to aberrant DNA methylation and gene silencing in angio-immunoblastic T-cell lymphoma

ENZYMES INVOLVED IN DNA METHYLATION

Methylation:
- DNMT1
- DNMT3A
- DNMT3B
- SAM

Demethylation:
- TET1
- TET2
- TET3
- O2

Cytosine (C) → 5-methylcytosine (5mC) → Hydroxymethylcytosine (5hmC)

MBD

Transcriptional Repression

Transcriptional Activity

Ch9: DNA Methylation in Aggressive Gastric Carcinoma, DOI: 10.5772/52135.
THREE PATHS TO ABERRANT METHYLATION

IDH1/2 INHIBITION
Redefining response in AML ASH 2015

- AG-221 – IDH2 Inhibitor
- NCT01915498
- >45 hour half life
- 198 patients, median age 69 years,
- 70% had an R140Q and 25% an R172K mutation in IDH2
- Objective responses were seen in 74 pts (41%), including 52 RR-AML pts (41%)

- AG-120 – IDH1 inhibitor
- NCT02074839
- 180 hour half-life
- Blood levels of 2HG normalising
- SD and PR in AML are clinically meaningful
- Responses are durable
- Differentiation evident in some patient WBC’s

DURATION OF AG-221 TREATMENT AND FIRST AND BEST RESPONSE IN RR-AML PATIENTS

Stein E, et al. Amer Soc Hematology 2015; Abst #323.
CLEARANCE OF mIDH1 ALLELE IN PATIENTS ON FIRST-IN-HUMAN STUDY OF AG-120 (NCT02074839)

78 patients enrolled
300 – 1200 mg qd. Recommended phase II dose = 500 mg qd.
AEs: diarrhea, fatigue, nausea (>30%)

Overall Response Rate 38.5 %, Complete Remission 11 pts (17.9%)

NGS assay for mIDH1 allele

In patients with CR, mIDH1 clearance: 3 of 11 pts

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HISTONE METHYLTRANSFERASES (KMTs): WRITERS

Aberrant histone methylation is a target for drug development

- KMTs
- Writers
- Alteration in cancer can be gain or loss of function
- Repressive
- Best known KMT is EZH2, specifically methylates lysine 27 of H3
  - EZH2 - H3K27Me3 methyltransferase – gain of function mutation
  - NSD2 H3K36Me2 methyltransferase – gain of function mutation
  - MLL fusion proteins recruit DOT1L – H3K79Me3 methyltransferase
  - SETD2 H3K36Me3 methyltransferase – loss of function mutation
EZH2 OVEREXPRESSION, MUTATION, OR TRUNCATION

Functionally different

Overexpression or activating mutation at Y641/646, A682G and A692V

- Increased methyltransferase activity and H3K27me3
  - Increased HDAC binding
- Aberrant gene repression
- Diffuse large B cell lymphomas have Y641/646 mutation

Phase 1 Study of tazemetostat (EPZ-6438), an inhibitor of enhancer of zeste-homolog 2 (EZH2): Preliminary safety and activity in relapsed or refractory non-hodgkin lymphoma (NHL) patients

<table>
<thead>
<tr>
<th>Relapsed or refractory NHL</th>
<th>Total (n=19)</th>
<th>Evaluable (n=15)</th>
<th>Best Response CR+PR(^a)</th>
<th>Best Response SD(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL GCB</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Non-GCB</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Undetermined</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>FL</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>MZL</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

The majority of objective responses occurred at the recommended Phase 2 dose of 800 mg BID. EZH2 status in patient tumours was determined, with 13/14 found to be wild-type (WT) and one patient, who experienced an ongoing PR at week 16, with an Y646H mutation.

\(^a\)Per IWG (Cheson, 2007), complete response (CR), partial response (PR), stable disease (SD)

GSK2816126, a highly selective and potent inhibitor of both wild type (wt) and mutant (mut) EZH2, decreases H3K27 tri-methylation, releases transcriptional repression of PRC2 target genes and induces anti-proliferative activity in several EZH2 wt/mut cancer cell lines

- 30 pts treated: 50 mg to 3000 mg (n=3) given IV twice weekly (3W-on/1W-off)
- Tumour types included 10 DLBCL, 2 tFL, 2 other NHL (FL and MZL) and 16 solid tumours
- No DLTs
- AE’s fatigue, nausea, vomiting, anaemia
- Of 22 pts: 1 PR in GCB+ DLBCL, 7 SD
- Expansion cohort to enroll patients with mutated EZH2
- Expansion dose: 3000 mg IV 2X/week (3W-on/1W-off)

HISTONE METHYLTRANSFERASES (KMTs): WRITERS

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GAIN OF FUNCTION MUTATIONS IN HISTONE METHYLTRANSFERASES EZH2 AND NSD2

EZH2

- **Y641/Y646**
  - Increased H3K27Me3
  - Lymphoma: DLBCL, FL

NSD2

- **E1099K**
  - Increased H3K36Me2
  - B-ALL E1099K
  - Myeloma t(4:14)

Rearranged MLL fusion proteins lose their H3K4 MT activity. The MLL fusion protein results in aberrant DOT1L recruitment. Previous studies of MLL-translocated leukaemia have found enhancement of H3K79 methylation at MLL fusion protein targets.

Pinometostat is a small molecule inhibitor of DOT1L with sub-nanomolar affinity

- 18 pts were enrolled on study
- 70 mg/m² as the recommended phase 2 dose (RP2D) in older pts.
- Pinometostat induced transient decreases in peripheral or marrow leukemic blasts in 7/18 pts, no objective responses
- H3K79me2 ChIP-Seq on leukemic blasts demonstrated that pinometostat induced reductions in methylation at MLL-r target genes (e.g. HOXA9 and MEIS1) of ≥ 80% at all post dose time points (15 and 28 days)
LOSS OF FUNCTION SETD2 MUTATIONS FOUND IN CANCER ARE ONCOGENIC

SETD2 is a H3K36Me3 lysine methyltransferase involved in DNA repair

CRITICAL EPIGENETIC REGULATORS

Are often altered or mutated in cancer and thus targets for therapy

<table>
<thead>
<tr>
<th>Writers</th>
<th>Erasers</th>
<th>Readers</th>
<th>Movers</th>
<th>Shapers</th>
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<tbody>
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<td>Acetylases, methylases, phosphorylases</td>
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<td>- TET2</td>
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<td>- SETD2</td>
<td>- HDAC</td>
<td>-</td>
<td>- ISWI</td>
<td>- H3F3A</td>
</tr>
<tr>
<td>- MLL</td>
<td>- KDM1A (LSD1)</td>
<td></td>
<td>- CHD</td>
<td></td>
</tr>
</tbody>
</table>

HISTONE DEACETYLASES (HDACs): ERASERS

Histone deacetylation is a proven target

- Histone deacetylases: HDACs
- Erasers
- Overexpression, closed chromatin
- Repressive
- HDACs classified into 4 groups of enzymes: I, Ila, IIb, IV
- HDAC Inhibitors: vorinostat, romidepsin, belinostat, panobinostat
- Global acetylation results from HDAC inhibition
- H3K9Ac, H3K18Ac, H3K23Ac, H3K56Ac, H4K5Ac, H4K8Ac, H4K16Ac
- Canonical mechanism: Open chromatin, induce gene expression
HDAC ENZYMES & INHIBITORS

Class I
HDAC1  482 aa
HDAC2  488 aa
HDAC3  428 aa
HDAC8  377 aa

Class IIa
HDAC4  1084 aa
HDAC5  1122 aa
HDAC7  855 aa
HDAC9  1069 aa

Class IIb
HDAC6  1215 aa
HDAC10 669 aa

Class III
SIRT1  747 aa

Class IV
HDAC11 347 aa

*Class I at doses administered
**Also inhibits HDAC 10
***Also inhibits class IIb

Romidepsin*  
Chidamide**  
Entinostat  
AR-42***  
CI-994

Vorinostat  
Belinostat  
Panobinostat  
Tefinostat  
Givinostat  
Abexinostat  
Quisinostat  
Ricolinostat

ACY-241

HISTONE MODIFICATIONS CONTROL GENE TRANSCRIPTION

Acetylation = Go signal for Gene Transcription

Deacetylation = Stop signal for Gene Transcription

Control of Cell Growth

Romidepsin Vorinostat Belinostat Panobinostat Chidamide

RESPONSE TO ROMIDEPSIN:
STAGE IVB, POST CVP

Screening

Cycle 5, Day 2

ROMIDEPSIN ACTIVITY IN CUTANEOUS T-CELL LYMPHOMA: RAPID, DURABLE

<table>
<thead>
<tr>
<th>Stage</th>
<th>N</th>
<th>ORR</th>
<th>CCR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GPI Study</strong></td>
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<td></td>
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</tr>
<tr>
<td>All</td>
<td>96</td>
<td>33 (34%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>≥ IIB</td>
<td>68</td>
<td>26 (38%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Duration</td>
<td>96</td>
<td>Median: 14.9 months</td>
<td></td>
</tr>
<tr>
<td><strong>NCI Study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>71</td>
<td>25 (35%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>≥ IIB</td>
<td>62</td>
<td>20 (32%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Duration</td>
<td>71</td>
<td>Median: 13.7 months</td>
<td></td>
</tr>
</tbody>
</table>

Two patients with CR durations ongoing: 45+, 127+ months

CTCL GENOMICS

Copy number changes instead of mutations:
9.1 deletions, 2.8 amplification, 1 mutation/tumour

CRITICAL EPIGENETIC REGULATORS

Are often altered or mutated in cancer and thus targets for therapy

- **Writers**
  - DNMT1
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- **Readers**
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  - HIST1H3B
  - H3F3A

HISTONE DEMETHYLASES (KDMs): ERASERS

Target for drug development

Erasers

Best known: LSD1 (KDM1A)

*demethylates* H3K4

LSD1 overexpressed in AML and MDS

Repressive

KDM inhibitors

- Tranylcypromine (TCP)
- Phenelzine
- IMG-7289
- GSK2879552
- INCB059872

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BROMODOMAIN PROTEINS: READERS

Mutated or altered in cancer: Targets for drug development

- Readers
- Read “Acetylation” marks
- BET (bromodomain and extra-terminal) proteins
- BRD4 is best known
- Mutations in BRD4 associated with Nutlin Midline Carcinoma
BRD4 “READS”
HYPERACETYLATION IN SUPERENHANCERS
Drives gene expression

BET INHIBITORS IN DEVELOPMENT

- JQ1 – tool compound

In ClinicalTrials.gov:

- I-BET 762 (GSK525762) – Phase I/II in NUT Midline Ca and Others
- GSK2820151
- OTX-015 (MK-8628) – Phase I in NUT Midline Ca; in leukaemia/lymphoma 5CR, 1 PR
- RO6870810/TEN-010 – 2 clinical trials, both recruiting
- CPI-0610 – 3 Phase I trials; Study for ORR in peripheral nerve sheath tumour
- SF1126
- RO6870810
- ABBV-075
- ZEN-3694
- INCB054329
- INCB057643
- BMS-986158

A Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of GSK525762 in Subjects With NUT Midline Carcinoma (NMC) and Other Cancers

This study is currently recruiting participants. (see Contacts and Locations)
Verified January 2017 by GlaxoSmithKline

ClinicalTrials.gov Identifier: NCT01587703
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CHROMATIN REMODELERS: MOVERS

Targets for drug development

- Movers
  - SWI/SNF complex
  - SMARC subunits
  - ARID1A, ARID1B
Table 1: SWI/SNF mutations in cancer

<table>
<thead>
<tr>
<th>SWI/SNF subunit</th>
<th>Associated cancers (mutation frequency)</th>
<th>Primary tumours or cell lines</th>
<th>Haploinsufficiency or homozygous inactivation</th>
<th>Types of mutations</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNF5</td>
<td>Rhabdoid tumours (98%)</td>
<td>Primary tumours and cell lines</td>
<td>Homozygous inactivation</td>
<td>Homozygous deletion, nonsense, missense and frameshift mutations</td>
<td>30–33</td>
</tr>
<tr>
<td></td>
<td>Familial schwannomatosis (30–40%)</td>
<td>Primary tumours</td>
<td>Homozygous inactivation</td>
<td>Truncating mutations</td>
<td>34,39,137–139</td>
</tr>
</tbody>
</table>

SWI/SNF-A

SMARCA2/4

SWI/SNF-B

PBRM1

ARID1A, AT-rich interactive domain-containing protein 1A (also known as BAF250A and SMARCF1); BRD7, bromodomain-containing 7; BRG1, BRM/SWI2-related gene 1 (also known as SMARCA4). *These cancers might represent rhabdoid tumours with atypical histological appearance. **These cancers carry large multi-gene deletions rather than SNF5- or BRD7-specific mutations.
ARID1A: CHROMATIN REMODELER FREQUENTLY MUTATED IN CANCER

TCGA Bioportal, http://www.cbioportal.org/
Cells with mutations in chromatin remodelers are uniquely sensitive to EZH2 inhibition.

EZH2 INHIBITOR ACTIVE IN SWI/SNF MUTANT CELLS

EZH2 INHIBITORS: TWO SEPARATE STRATEGIES

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EPIGENETICS DRUG PORTFOLIO

DNA methyltransferase
IDH1/2
Histone deacetylase
Histone methyltransferase
Histone demethylase
Bromodomain
Chromatin remodelers
Numerous reports have shown that various components of the immune response are upregulated after DNMT and or HDAC inhibition:

- Components of the MHC complex
- Cytokines important for the immune response
- Response to viral RNA
- PD-L1

Is there a wider role in immunotherapy?
EPIGENETIC AGENTS UPREGULATE MANY COMPONENTS OF THE IMMUNE RESPONSE

Potentially enhancing immunotherapy


Upregulation of tumour associated antigen; TAP1/2; chaperones; MHC class I and class II molecules; the CD40, CD80, CD86, and ICAM1 costimulatory/accessory molecules; the NKG2D ligands MICA, MICB and ULBP; and death receptors (e.g., FAS).
EPIGENETIC AGENTS IN DEVELOPMENT

- Writers, Erasers, Readers, Movers – Agents have entered clinical testing
- DNA methyltransferase inhibitors and histone deacetylase inhibitors have gained U.S. FDA approval
- Most activity to date is in haematological or lymphoid malignancies
- Serves as “proof of concept”
- Seemingly small changes play critical role in cancer development
  - e.g. SETD2 – loss of the 3rd methyl group
- An epigenetic mutation may be a “founder mutation” and inhibition may be insufficient to really affect the malignancy if other oncogenic drivers have emerged
- Work is needed to translate findings to solid tumours
- Combinations need to be studied
- If there are 700 “epigenes”, how many are critical in cancer? How many targets?
- How many agents in development do we really need for the same target?
- Is there a wider role in immunotherapy?
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