COR2ED
THE HEART OF MEDICAL EDUCATION
MOVING FROM PARP INHIBITION TO TARGETING DNA REPAIR AND DNA DAMAGE RESPONSE IN CANCER THERAPY

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SELECTED HIGHLIGHTS

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DNA DAMAGE RESPONSE (DDR) IS OF CRUCIAL IMPORTANCE AS A CANCER TARGET

DDR coordinates the identification, signaling, and repair of DNA damage. PARP is the most well-known therapeutic target and several other targets are being investigated for the treatment of cancer.

**DNA damage**
- Single strand breaks
- Double strand breaks
- UV bulky adducts
- Single nucleotide mutations

**Signaling pathways**
- PARP1/2
- ATM
- ATR
- CHK1/2
- DNA-PK
- WEE1
- MLH1/2*
- MSH2/6*

**Effectors**
- PARP*
- RAD51*
- POLQ*

**DNA repair**
- BER
- HRR
- NHEJ
- MMEJ
- NER
- MMR

<table>
<thead>
<tr>
<th>Pharmacologically targeted:</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARP1/2 Olaparib (AstraZeneca)</td>
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<tr>
<td>Rucaparib (Clovis)</td>
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<tr>
<td>Niraparib (Tesarro)</td>
</tr>
<tr>
<td>Talazoparib (Pfizer)</td>
</tr>
<tr>
<td>ATR AZD-6738 (AstraZeneca)</td>
</tr>
<tr>
<td>M-4344 (Merck)</td>
</tr>
<tr>
<td>DNA-PK Asi DNA (Onxeo)</td>
</tr>
<tr>
<td>CC-125 (Celgene)</td>
</tr>
<tr>
<td>LY-3023414 (Eli Lilly)</td>
</tr>
<tr>
<td>M-3814 (Merck)</td>
</tr>
<tr>
<td>WEE1 AZD-1775 (AstraZeneca)</td>
</tr>
<tr>
<td>CHK1/2 CBP-501 (CanBas)</td>
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<tr>
<td>Prexasertib (Eli Lilly)</td>
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<tr>
<td>GDC-0575 (Genentech)</td>
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<tr>
<td>SRA-737 (Sierra Oncology)</td>
</tr>
<tr>
<td>ATM AZD-0156 (AstraZeneca)</td>
</tr>
</tbody>
</table>

*Inhibitors in preclinical development

BER, base excision repair; DDR, DNA damage response; HRR, homologous recombination repair; MMEJ, micro-homology mediated end joining; MMR, mismatch repair; NER, nucleotide excision repair; NHEJ, non-homologous end joining; PARP, poly (ADP-ribose) polymerase
PARP INHIBITION IN THE TREATMENT OF CANCER

- Four PARP inhibitors have been approved for use in the treatment of ovarian and breast cancer in Europe and the USA.

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>Breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance therapy</td>
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<tr>
<td>Olaparib</td>
<td>Olaparib</td>
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<tr>
<td>Niraparib</td>
<td>Talazoparib</td>
</tr>
<tr>
<td>Rucaparib</td>
<td></td>
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</tbody>
</table>

- The therapeutic reach of PARP inhibitors is expanding to other cancer types, many of which are associated with BRCA mutations.
  - Trials are ongoing in pancreatic, endometrial, prostate, urothelial, colorectal, glioblastoma, small-cell and non-small-cell lung and gastroesophageal cancers.
THE FUTURE ROLE OF PARP INHIBITION IN CLINICAL PRACTICE

Selecting the right patients

• Patients whose tumors harbor BRCA mutations are likely to respond to PARP inhibition, and identifying these patients is now well established in the clinic
  – In ovarian cancer, platinum sensitivity functions as a surrogate marker for HRD

• Genomic scars and mutational signatures associated with an HRD phenotype can define a wider population that may benefit from DDR targeting agents

• Understanding innate tumor genomics prior to treatment and combining this knowledge with information from functional analysis assessing sensitivity to PARP inhibition may be applied to generate patient-personalized treatment plans

DDR, DNA damage response; HRD, homologous recombination repair defects
THE FUTURE ROLE OF PARP INHIBITION IN CLINICAL PRACTICE

Understanding resistance

- Several mechanisms of acquired PARP inhibitor resistance have been described in pre-clinical settings
  - To date, only restoration of HRR and expression of hypomorphic forms of BRCA1 have been shown to be clinically relevant
- It is likely that in different cancers, different mechanisms of resistance may emerge, likely depending on the germline or other mutational profile, or other factors such as origin of the disease or prior treatment
  - These mutations may include loss of PARP1 expression, compromised regulation of end-resection via loss of 53BP1, MAD2L2/Rev7 or the Shieldin complex, and activation of trans-lesion DNA synthesis through loss of CHD4, allowing less efficient HRR to proceed

HRR, homologous recombination repair
MOVING FROM PARP TO DDR INHIBITION IN THE CLINIC

Trapping PARP on DNA following its inhibition confers lethality to HRR deficient cells. This concept has been exploited in the clinic and can be applied to other molecules in the DDR pathway.
The three key cell cycle checkpoints are being targeted by small molecule inhibitors in clinical trials. Cancer cells have increased susceptibility to S-phase-induced DNA damage that in turn may lead to either replication catastrophe or apoptosis (unsustained levels of S-phase DNA damage), or mitotic catastrophe (double strand breaks carried into mitosis).

**G2/M Checkpoint**
- **DDR Targets**: CHK1, WEE1

**S phase Checkpoint**
- **DDR Targets**: ATR, CHK1, DNA-PK, WEE1

**G1/S Checkpoint**
- **DDR Targets**: ATM, CHK2, p53

**DDR Targets**
- **ATR**
  - Agent: AZD-6738 (AstraZeneca)
  - Agent: M-4344 (Merck)
  - Agent: M6620 (Merck)
- **DNA-PK**
  - Agent: Asi DNA (Onxeo)
  - Agent: CC-125 (Celgene)
  - Agent: LY-3023414 (Eli Lilly)
  - Agent: M-3814 (Merck)
- **WEE1**
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- **CHK1/2**
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  - Agent: AZD-0156 (AstraZeneca)

**Activity in Cell Cycle**
- **ATR**
  - Kinase activated by replication stress and required to coordinate replication fork stabilisation and restart
- **DNA-PK**
  - DNA double strand break responsive kinase important for DNA repair by non-homologous end joining
- **WEE1**
  - Kinase that negatively regulates the G2-M transition and entry into mitosis
- **CHK1/2**
  - DNA damage responsive effector kinases, which work downstream of ATR and ATM, respectively
- **ATM**
  - Kinase that initiates the checkpoint response to DNA double strand break required to signal to the DNA repair and cell cycle machineries
## FUTURE DDR TREATMENT STRATEGIES

### Compounds targeting DDR in clinical development (other than PARP1/2 inhibitors)

<table>
<thead>
<tr>
<th>DDR Target</th>
<th>Compound Name</th>
<th>Company Name</th>
<th>Highest Development Stage</th>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>CHK1/2</td>
<td>CBP-501</td>
<td>CanBas Co Ltd</td>
<td>Phase II</td>
<td>NSCLC</td>
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<tr>
<td></td>
<td>Prexasertib</td>
<td>Eli Lilly and Company</td>
<td>Phase II</td>
<td>SCLC, Ovarian Cancer, Triple Negative Breast Cancer, Metastatic Castrate Resistant Prostate Cancer</td>
</tr>
<tr>
<td></td>
<td>GDC-0575</td>
<td>Genentech</td>
<td>Phase I</td>
<td>Solid tumors</td>
</tr>
<tr>
<td></td>
<td>SRA-737</td>
<td>Sierra Oncology Inc</td>
<td>Phase I</td>
<td>Solid tumors</td>
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<tr>
<td>WEE1</td>
<td>AZD1775</td>
<td>AstraZeneca</td>
<td>Phase II</td>
<td>SCLC, Squamous Cell Lung Cancer, Ovarian Cancer, Triple Negative Breast Cancer, Advanced Acute Myeloid Leukaemia or Myelodysplastic Syndrome, Gastric Cancer, Head and Neck Cancer, Pancreatic Cancer</td>
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<tr>
<td>ATR</td>
<td>AZD6738</td>
<td>AstraZeneca</td>
<td>Phase I</td>
<td>Various solid malignancies</td>
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<tr>
<td></td>
<td>M-4344</td>
<td>Merck KGaA</td>
<td>Phase I</td>
<td>Various solid malignancies</td>
</tr>
<tr>
<td></td>
<td>M6620 (VX-970)</td>
<td>Merck KGaA</td>
<td>Phase II</td>
<td>Various solid malignancies</td>
</tr>
<tr>
<td>DNA-PK</td>
<td>CC-115</td>
<td>Celgene Corp</td>
<td>Phase II</td>
<td>Glioblastoma</td>
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<td>LY-3023414</td>
<td>Eli Lilly and Company</td>
<td>Phase II</td>
<td>SCLC, Endometrial Cancer, Prostate Cancer, Pancreatic Cancer, Lymphoma</td>
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<tr>
<td></td>
<td>AsiDNA</td>
<td>Onxeo SA</td>
<td>Phase I</td>
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**NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer**
## OPPORTUNITIES FOR COMBINATION THERAPY WITH DDR-TARGETING COMPOUNDS

Trials are underway combining compounds targeting DDR, including PARP inhibitors, with:

<table>
<thead>
<tr>
<th>Other DDR-targeting agents, including:</th>
<th>Angiogenesis inhibitors, including:</th>
<th>Immunotherapy, including:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ATR inhibitors</td>
<td>• VEGF and VEGF-A inhibitors</td>
<td>• Anti-PD-1 antibodies</td>
</tr>
<tr>
<td>• WEE1 inhibitors</td>
<td></td>
<td>• Anti-PD-L1 antibodies</td>
</tr>
</tbody>
</table>

PD-1, programmed death protein 1; PD-L1, programmed death-ligand 1; VEGF, vascular endothelial growth factor
OVERCOMING CHALLENGES IN DDR INHIBITION

- The optimal treatment sequence of DDR inhibitors with other agents is still being determined
  - Results from the SOLO 1 trial suggest moving PARP inhibitors/DDR agents earlier in the treatment course may be appropriate for certain patients
- Understanding the differences between the mechanisms of action for different PARP inhibitors and the influence of specific BRCA mutations on efficacy will be important to support the future development of DDR inhibitors
- DDR-targeting agents will be tailored for specific patient populations and for specific innate and acquired mechanisms of resistance

<table>
<thead>
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<th>Key questions for the near future:</th>
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<tr>
<td>Defining the genetic and epigenetic level of HRD</td>
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