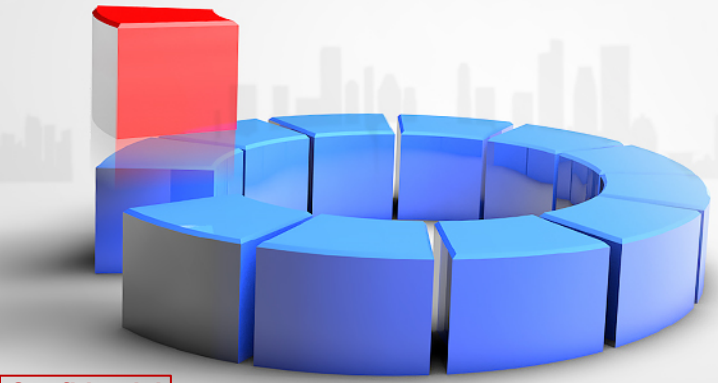
“Anticancer drug development with ADP-ribose regulatory platform”

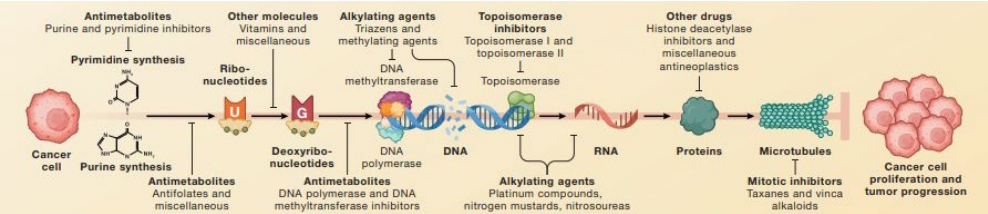
PearlsInMires
Who would have thought what we are thinking?

The innovative concept of our technology



Anticancer drug development focusing on inhibitor type

Inhibitors targeting known cancer cell survival pathways



Cell, 186, 8, P1515-1516, 2023

PARP inhibitors approved by USFDA or EMA

CLOVIS ONCOLOGY

AstraZeneca MERCK

gsk

Many inhibitors under development

Selected projects targeting synthetic lethality*				
Project	**Company**	**Mechanism**	**Trial**	**Note**
TNG908	Tango Therapeutics	PRMT5 inhibitor	Ph1/2 in solid tumours with MTAP deletion	Initial data due H1 2023
MRTX1719	Mirati	PRMT5 inhibitor	Ph1/2 in solid tumours with MTAP deletion	Ends Jan 2024
SKL27969	SK Biopharmaceuticals	PRMT1 inhibitor	Ph1/2 solid tumours	Ends Sep 2024
AMG 193	Amgen	PRMT5 inhibitor	Ph1 in solid tumours with MTAP deletion	Separate clinical trial collaboration with Ideaya's IDE397
AG-270	Servier (ex Agios)	Mat2A inhibitor	Ph1 in tumours with MTAP deletion	Servier bought Agios's oncology business in 2020
IDE397	Ideaya	Mat2A inhibitor	Ph1 in solid tumours with MTAP deletion	"ctDNA molecular responses" claimed; GSK declined option
JNJ-64619178	Johnson & Johnson	PRMT5 inhibitor	Ph1 in various tumours	Was due to end mid-2022
PRT543	Prelude Therapeutics	PRMT5 inhibitor	Ph1 in various tumours	1 CR in 26 evaluable solid tumour & lymphoma subjects
PRT811	Prelude Therapeutics	PRMT5 inhibitor	Ph1 in various tumours	0 responses in 19 solid tumour (incl glioma) subjects
RP-6306	Repare Therapeutics	PKMYT1 inhibitor	Three ph1 studies	Incl combo with RP-3500 (ATR inhibitor licensed to Roche)
GSK3326595	GSK/Epizyme	PRMT5 inhibitor	Discontinued in ph1	Deal canned by GSK, Epizyme bought by Ipsen
GSK3368715	GSK/Epizyme	PRMT1 inhibitor	Discontinued in ph1	Deal canned by GSK, Epizyme bought by Ipsen
PF-06939999	Pfizer	PRMT5 inhibitor	Discontinued in ph1	"Strategic decision within the Pfizer oncology portfolio"
JBI-778	Jubilant Pharmova	PRMT5 inhibitor	NA	IND cleared Aug 2022
TNG462	Tango Therapeutics	PRMT5 inhibitor	NA	IND filing due H1 2023
ISM020	Insilico Medicine	Mat2A inhibitor	NA	IND filing due 2023
AGX323	Angex Pharmaceutical	PRMT5 inhibitor	NA	AACR data in 2021
AT101/ AT201	Argonaut Therapeutics	PRMT5 inhibitor	NA	Several preclinical leads

*Note: *for a list of Wee1 and ATR inhibitors see recent Evaluate Vantage coverage. Source: company statements, Evaluate Pharma & clinicaltrials.gov.*

Is suppression the only answer?

Common problems of conventional drugs:
Adverse effect, low tolerability, and resistance to therapies

PearlsInMires wonders why suppression is the only way to develop anticancer drug.

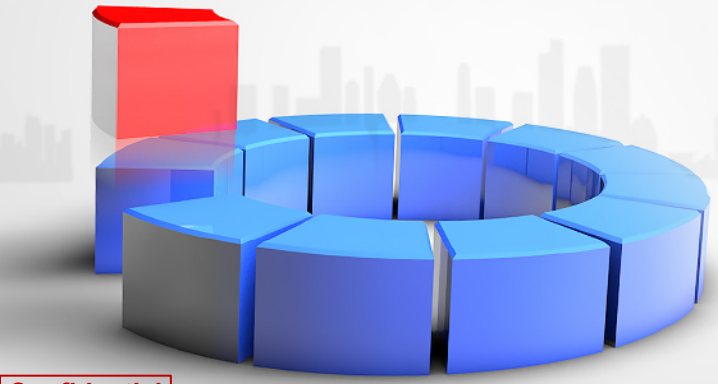
An innovative concept for developing anticancer drug

Obviously, there will be a target to induce anticancer effect without suppression.

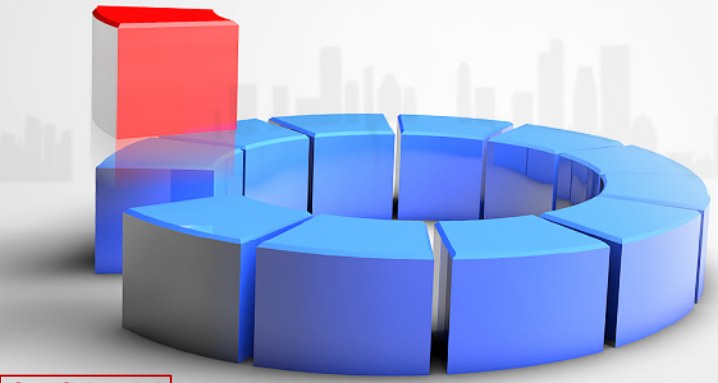
- **Concept:** Breaking away from the stereotype of the existing 'inhibitor-types'
- **Target:** 'Essential factor for cancer cell survival', but 'Unfavorable for cancer cell survival by target expression'
- **Development Requirements**

  1. First-in-class drug inducing cancer cell death by 'Target sustaining'
  2. Clear MoA and easy PoC
  3. Easy to select optimal indications in clinical

Four categories for development of the ADP-ribose regulatory platform



Category 1: Synthetic lethality intervention by the platform technology



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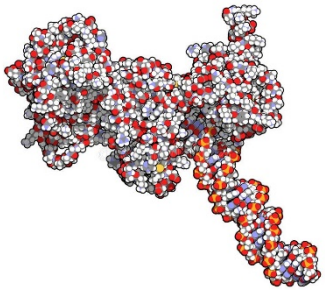
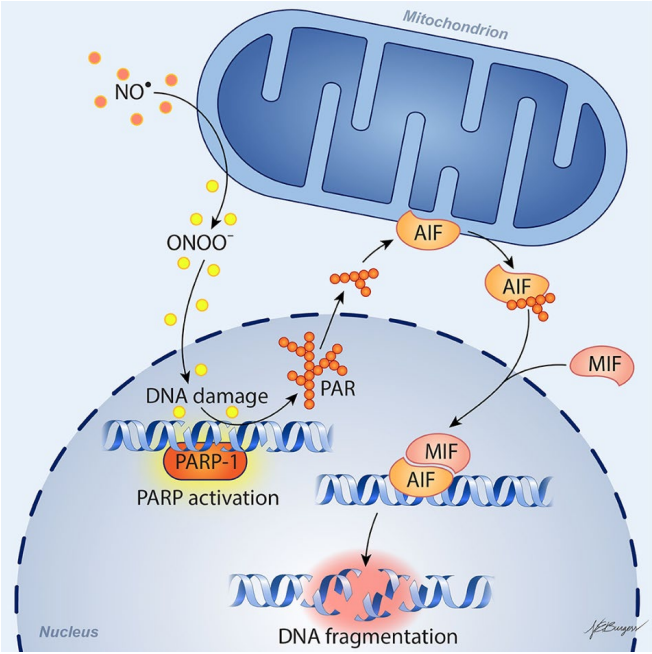
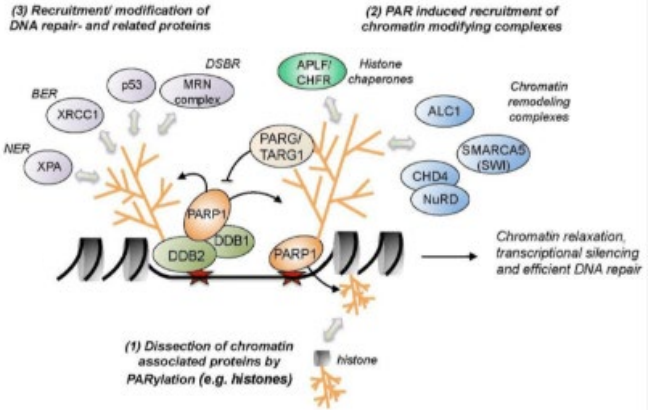


ADP-ribose
- **DNA damage response**
- Epigenetic control
- Cell Signaling
- Regulation of gene expression
- Stress response
- **Parthanatos**

Category 1: Synthetic lethality intervention (Parthanatos/DNA damage)

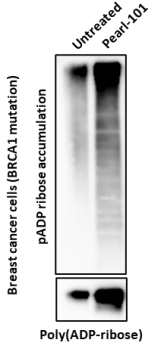


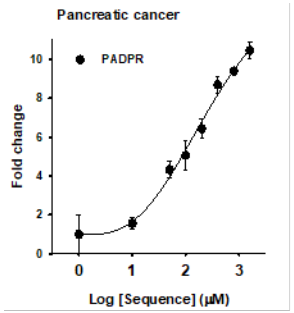
Front Neurol . 2021 May 5;12:662034.

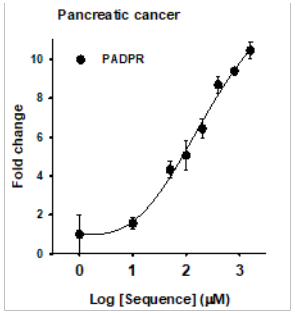


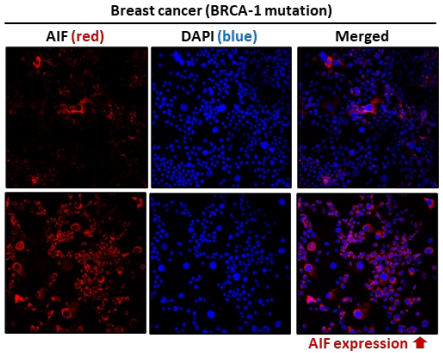
Int J Mol Sci . 2017 Aug 5;18(8):1715

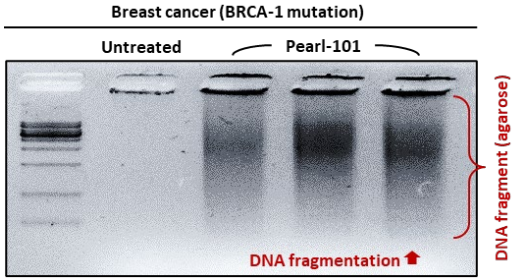
Category 1: Synthetic lethality intervention by the platform technology

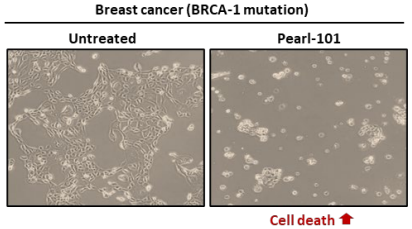


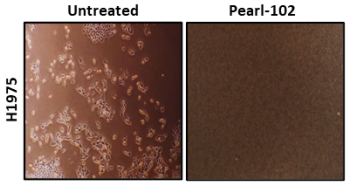


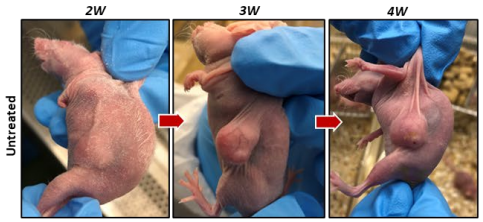


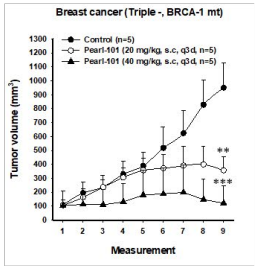


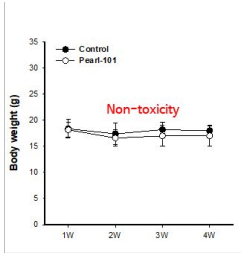


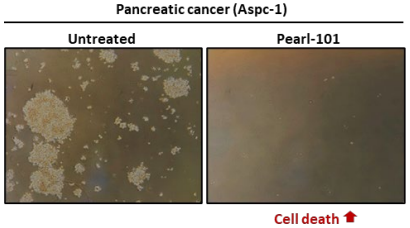


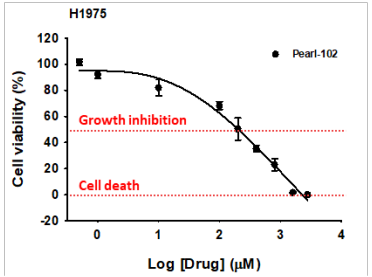


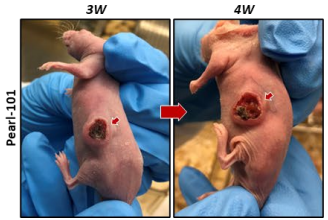


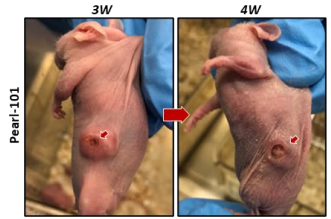


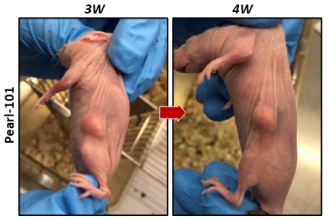




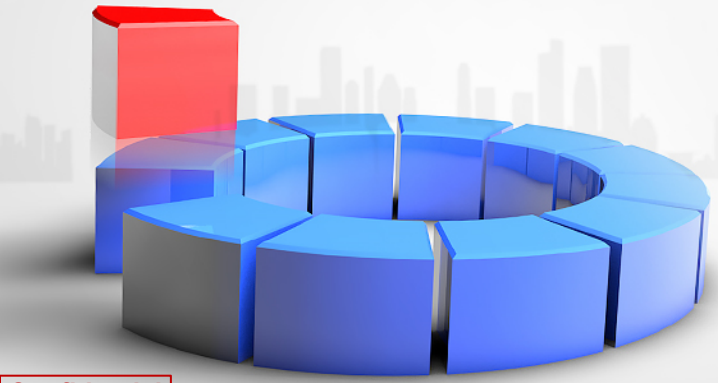




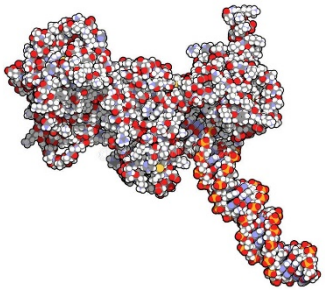




Category 2: Chromatin-structure modulation by the platform technology



Category 2: Chromatin-structure modulation by the platform technology (8 items secured)



ADP-ribose
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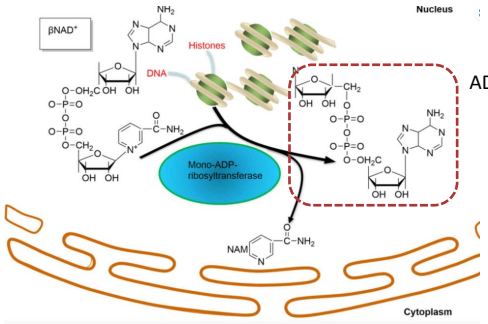
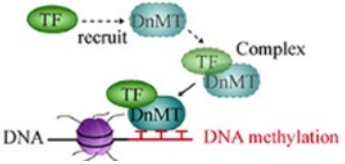
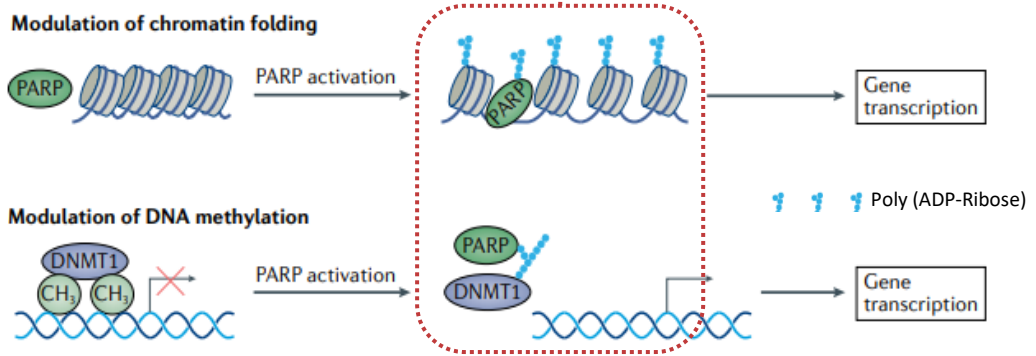
Category 2: Chromatin-structure modulation (Epigenetic control)



Exp Ther Med . 2021 Jun;21(6):577.

ADP-Ribose

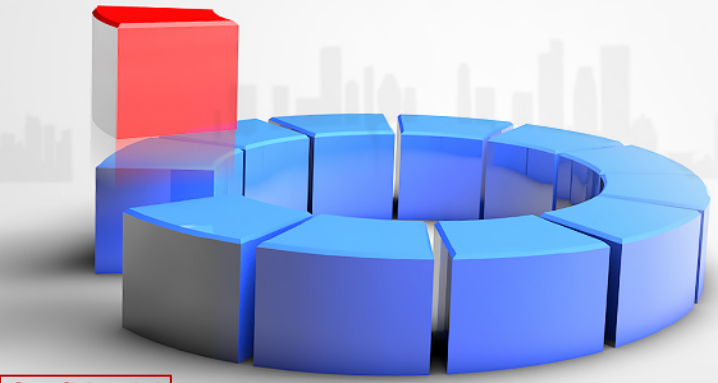




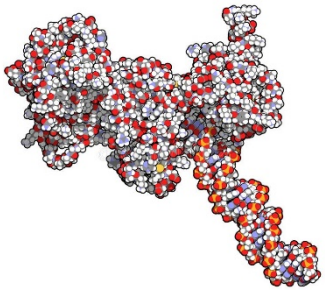
DNMT: DNA (cytosine-5)-methyltransferase 1

Nat Rev Drug Discov . 2020 Oct;19(10):711-736.

Category 3: Regulation of cell signaling and protein degradation by the platform technology



Category 3: Regulation of cell signaling and protein degradation by the platform technology (19 items secured)



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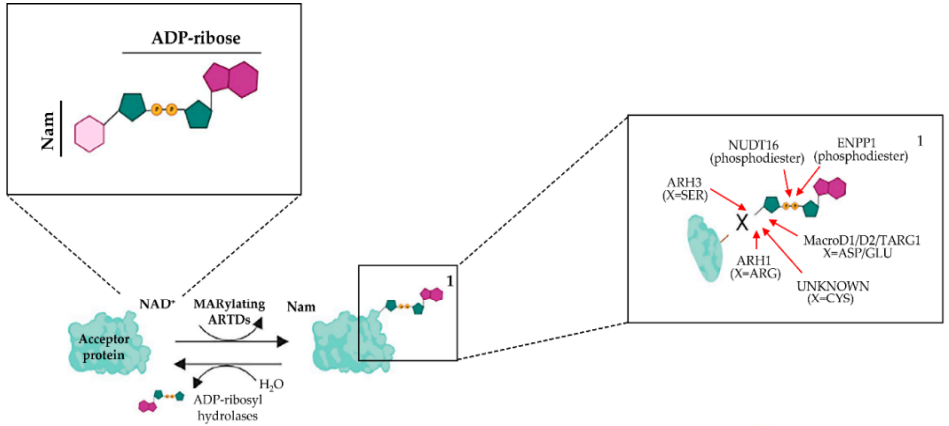
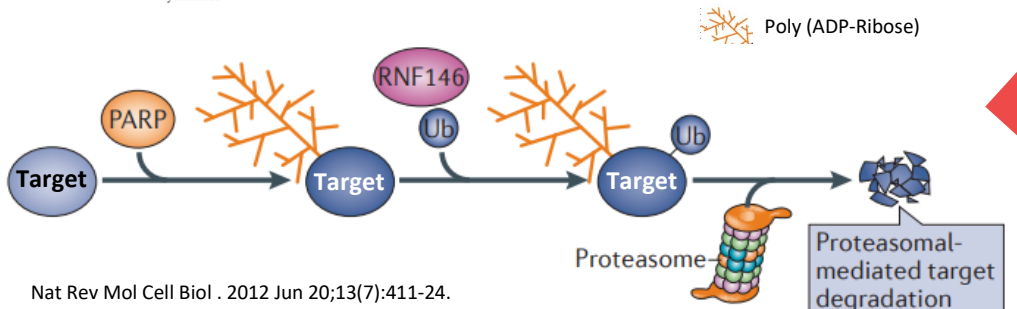


Biomolecules . 2022 Mar 13;12(3):443.



Nat Rev Mol Cell Biol . 2012 Jun 20;13(7):411-24.

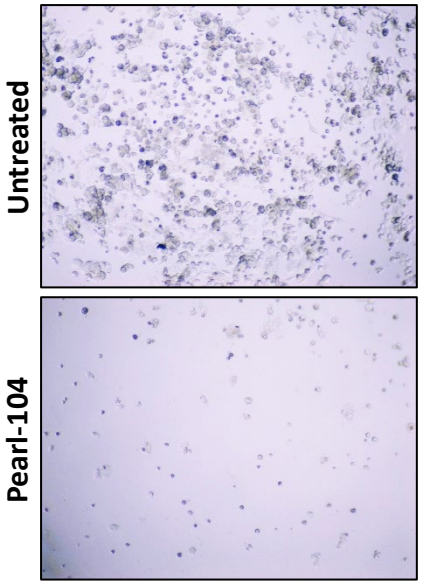
Category 3: Regulation of cell signaling and protein degradation by the platform technology (19 items secured)

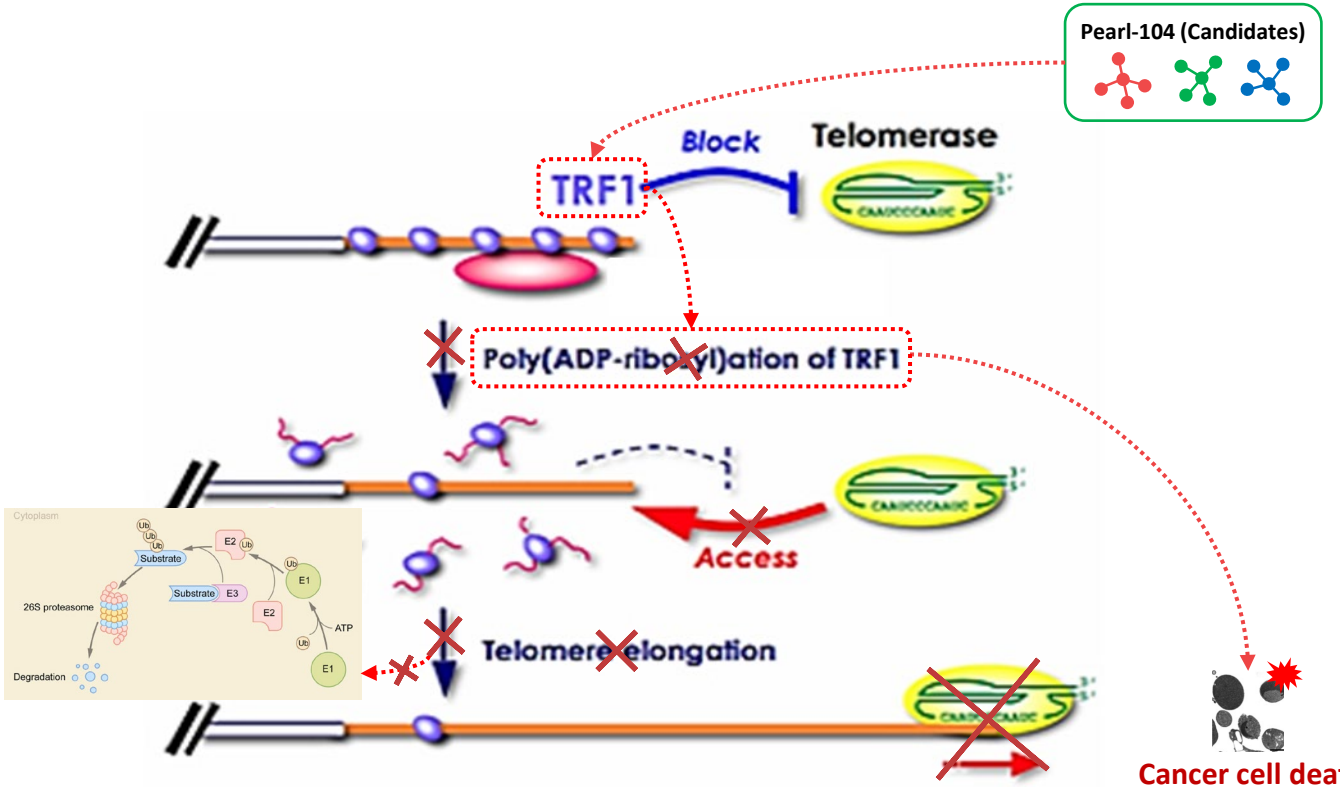
Pearl-104

Peptide-based TRF-1 conservation drug

First-in-class drug
Acting directly on the target in cancer cells

Aspc-1 (Pancreatic cancer)





TRF1: Telomeric repeat binding factor 1

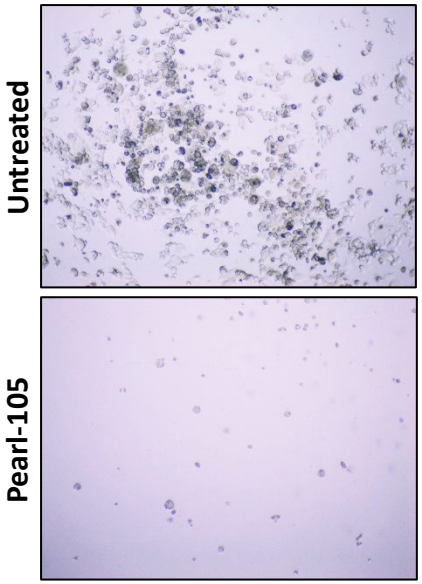
Category 3: Regulation of cell signaling and protein degradation by the platform technology (19 items secured)

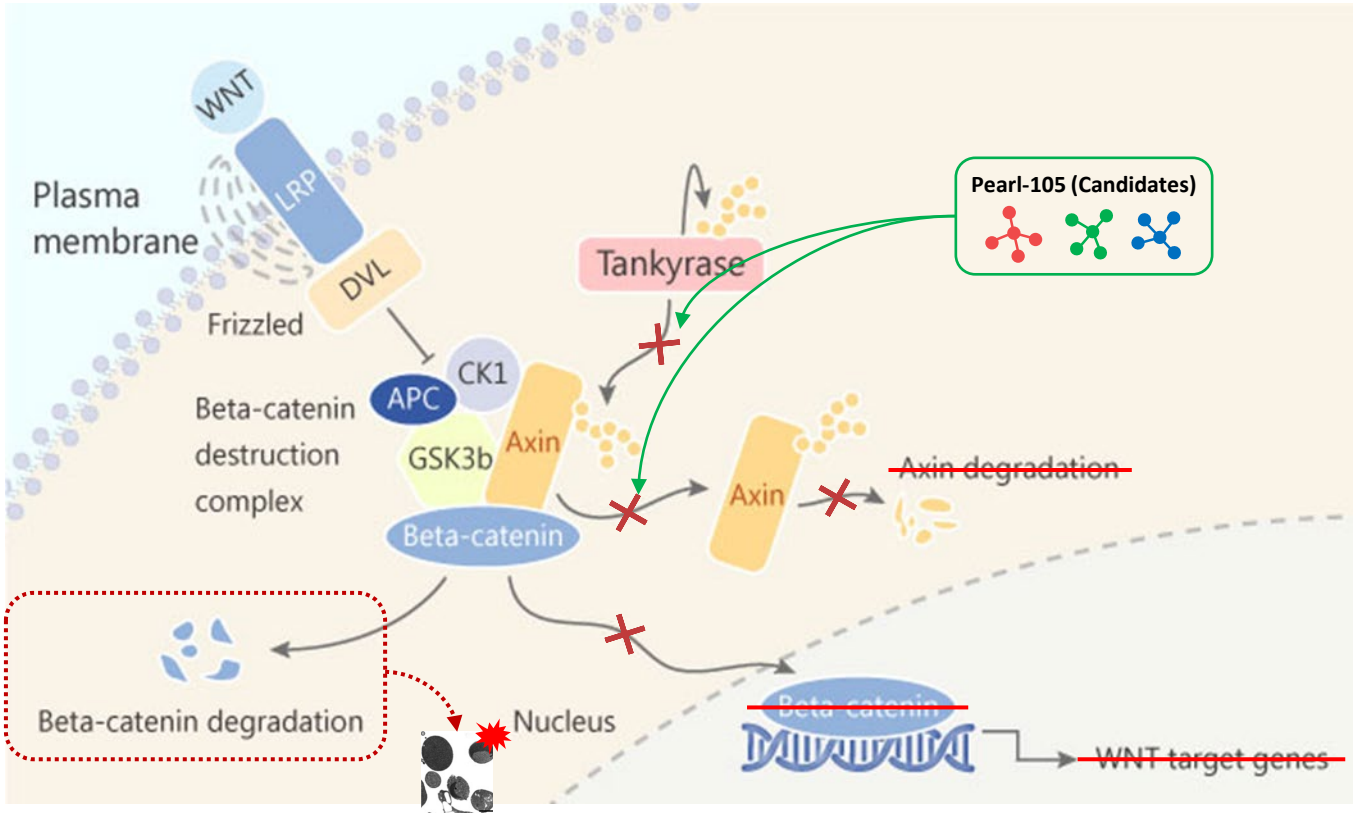
Pearl-105

Peptide-based Axin1 conservation drug

First-in-class drug
Acting directly on the target in cancer cells

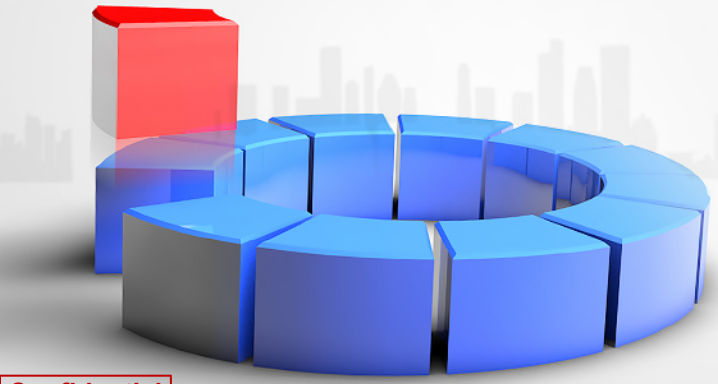
Aspc-1 (Pancreatic cancer)





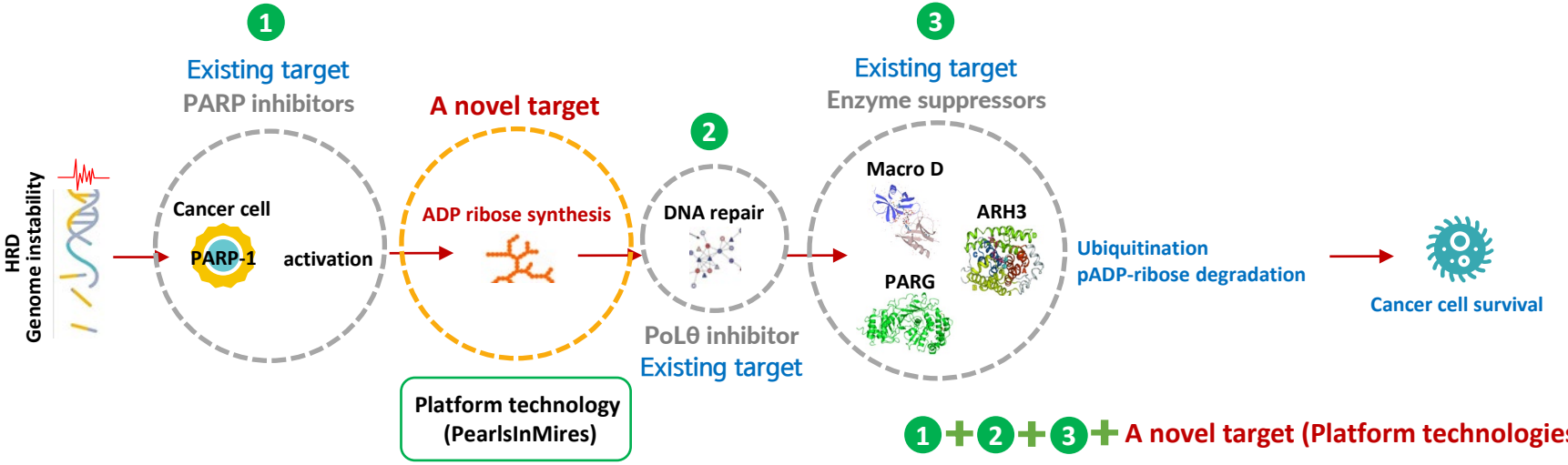
Cancer cell death

Competitiveness of the platform technology



Opportunities to develop in combination with the existing drugs

First-in-class that does not share previously known mechanism of existing drugs.
There is high possibility to cooperate with other pharmaceutical companies.



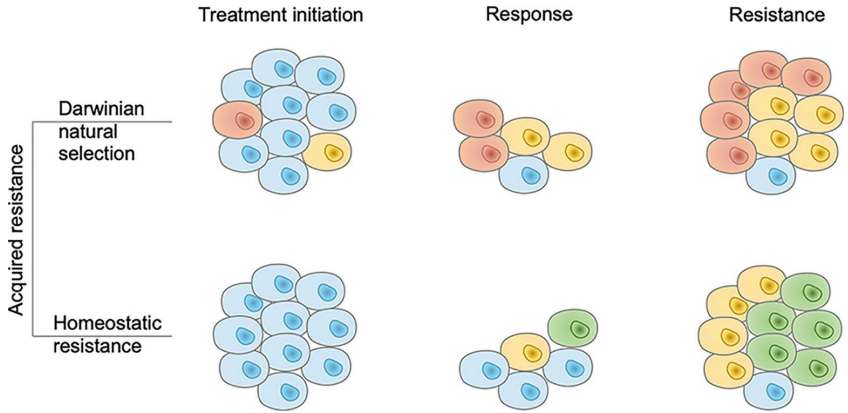
1 + 2 + 3 + A novel target (Platform technologies)

PARP: Poly (ADP-ribose) polymerase
ADP: adenosine diphosphate
Macro D: Macro domain
PARG: Poly(ADP-Ribose) Glycohydrolase
ARH3: ADP-ribosylhydrolase 3

Potential of complimenting or replacing the existing anticancer drugs

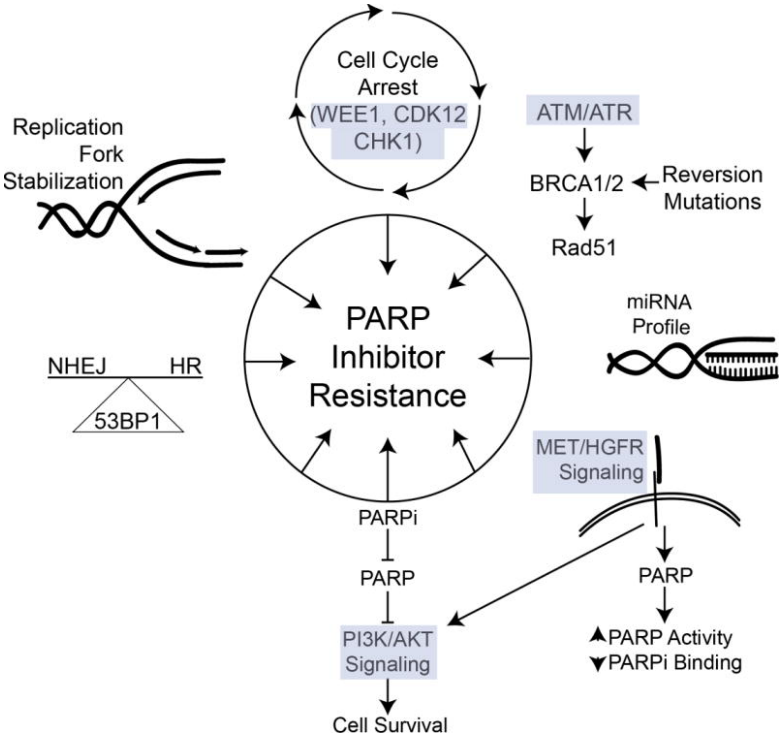
Our platform technology can show anticancer effect regardless resistance to existing anticancer drugs

Common resistant mechanism (Chemo-, Immuno-, target therapies)



Front Immunol . 2021 Jun 14;12:693609

Gynecologic Oncology, 14 Oct 2017, 147(3):695-704

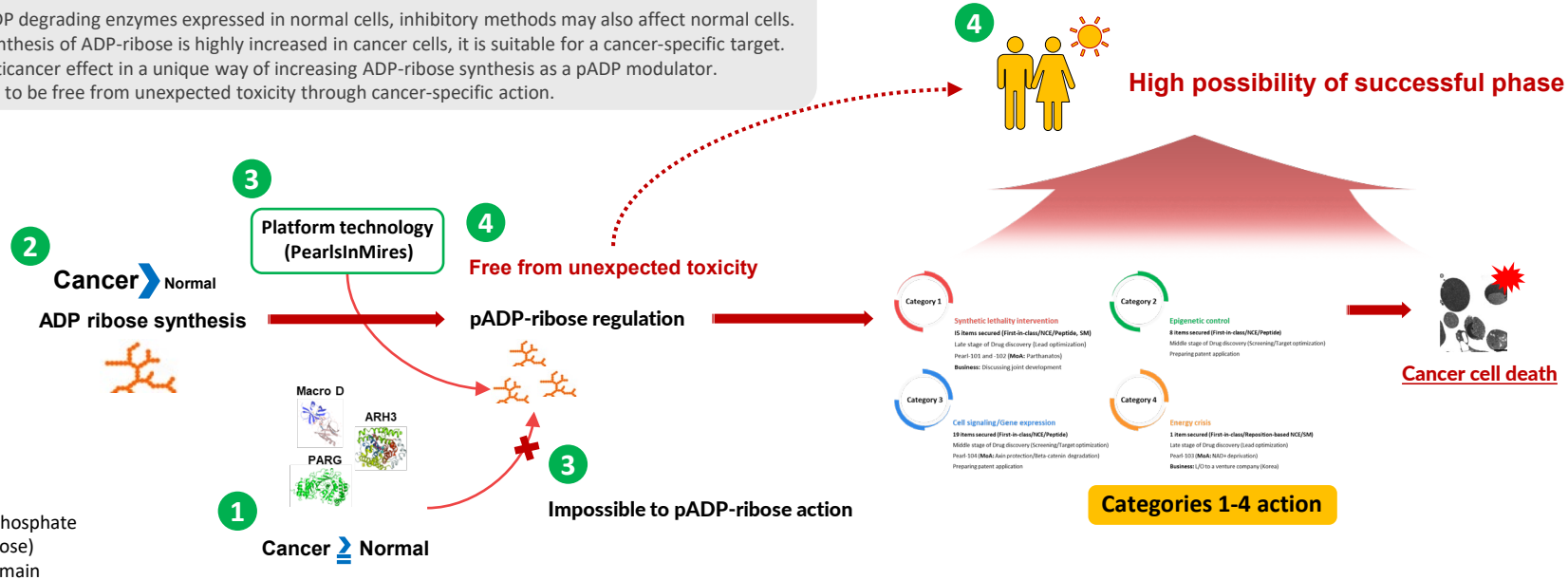


High probability of successful phase 1 clinical trial

High probability of successful phase 1 clinical trial by cancer-specific action.

Key points in a solution

1. Since the ADP degrading enzymes expressed in normal cells, inhibitory methods may also affect normal cells.
2. Since the synthesis of ADP-ribose is highly increased in cancer cells, it is suitable for a cancer-specific target.
3. Inducing anticancer effect in a unique way of increasing ADP-ribose synthesis as a pADP modulator.
4. It is possible to be free from unexpected toxicity through cancer-specific action.



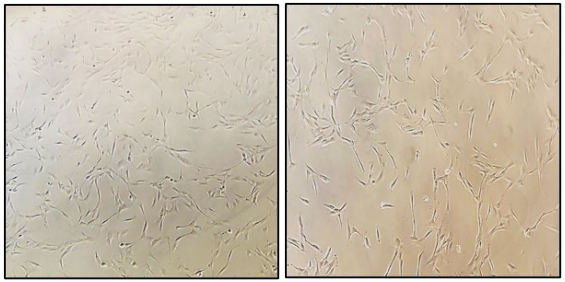
ADP: adenosine diphosphate
pADP: Poly(ADP-ribose)
Macro D: Macro domain
PARG: Poly(ADP-Ribose) Glycohydrolase
ARH3: ADP-Ribosylhydrolase 3

High probability of successful phase 1 clinical trial

The drugs are non-toxic to normal cells and healthy mice (non-official GLP toxicity data).

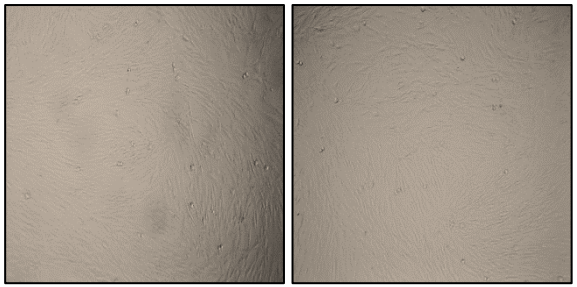
No toxicity was observed.

Untreated | Pearl-101



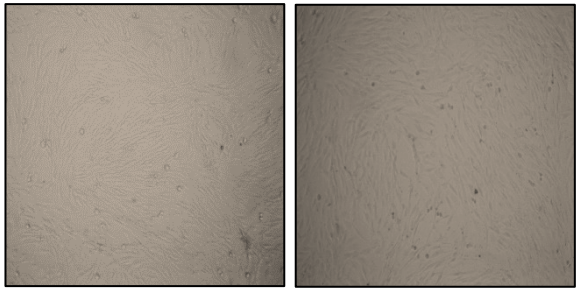
CCD-18Co (Normal colon fibroblast)

Untreated | Pearl-104



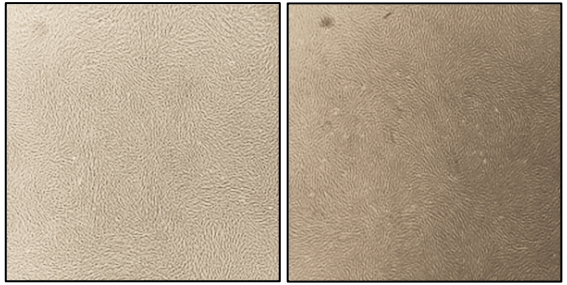
HFDPS (Human normal follicle dermal papilla cells)

Untreated | Pearl-105



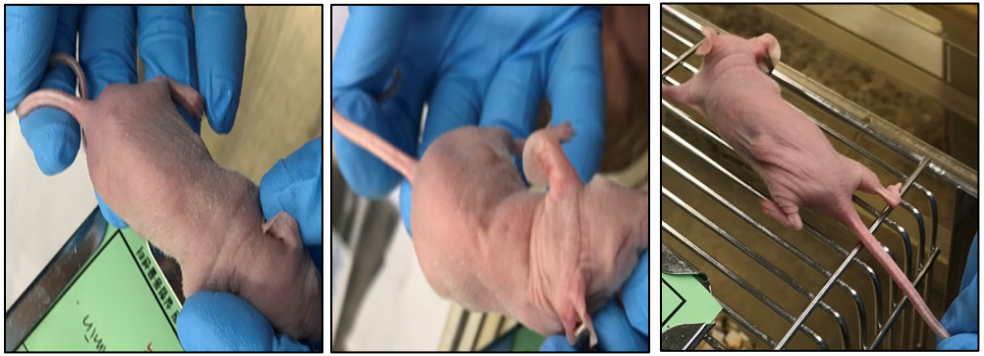
HFDPS (Human normal follicle dermal papilla cells)

Untreated | Pearl-102



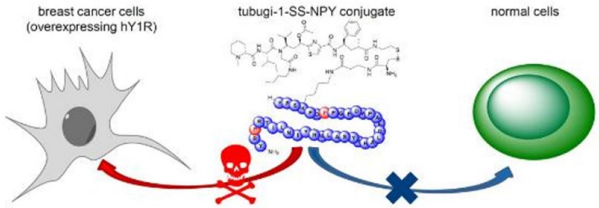
HFDPS (Human normal follicle dermal papilla cells)

Untreated | Pearl-101 | Pearl-102

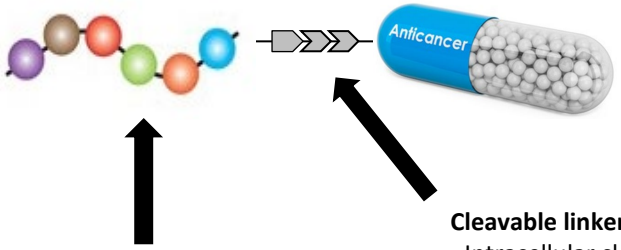


Excellent extensibility as the platform technology

Applicable to develop various new formulations by conjugating a novel and/or the existing drugs



Anti-cancer peptides + Cancer specific sequences

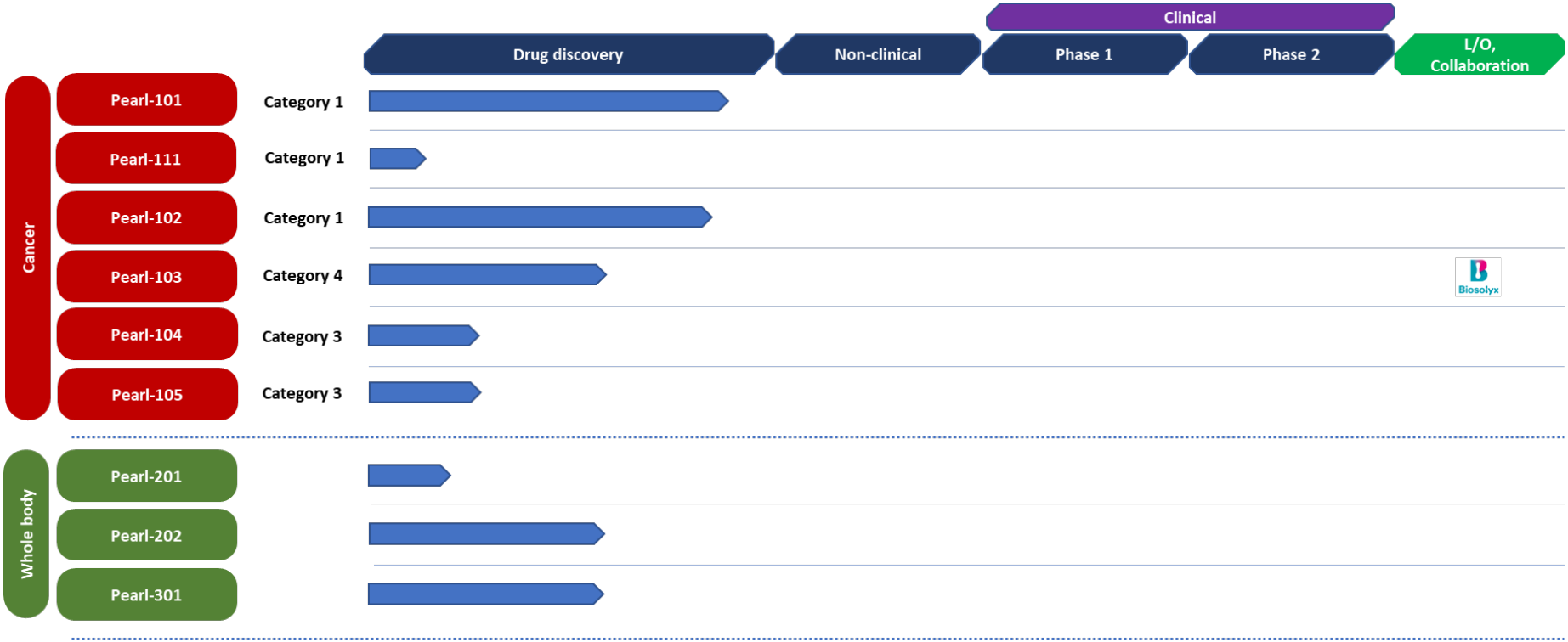


Cytostatic/Cytotoxic Payload

Anti-cancer/Tumor targeting peptide
- Amino acid modification
- PEGylation, etc.
- Improving anticancer activity

Cleavable linker
- Intracellular cleavability
- Stable transport until tumor cells are reached
- Disulfide linkage, etc.

Pipeline


Clinical
Drug discovery
Non-clinical
Phase 1
Phase 2
L/O, Collaboration
Cancer
Pearl-101
Category 1
Pearl-111
Category 1
Pearl-102
Category 1
Pearl-103
Category 4
Biosolyx
Pearl-104
Category 3
Pearl-105
Category 3
Whole body
Pearl-201
Pearl-202
Pearl-301

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