Hyperthermia and immune modulation in homologous recombination stratified epithelial ovarian cancer: Rationale for developing a clinical trial of HIPEC vs IP Chemotherapy with translational end points and a targeted therapy approach

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Origin of proposal: Previous and ongoing work:

Bench Clinic Bench

(Mukhopadhyay et al . Clin Cancer Research 2010; Cancer Res 2012)

Functional assay of Homologous recombination (HR) deficiency from primary tissue material

50% EOC are HRD and have better chemoresponse to platinum/Parp inhibitor as well as higher incidence of achieving optimal surgical resection

	HRC (24)	HRD (26)	
Complete /optimal cytoreduction	62.5%	80.8%	
CA 125 at presentation (median)	427	2079.50	0.007*
Serous Histology	62.5%	92.3%	0.035*
Platimun Sensitive	16.7%	53.8%	
Sensitivity to PARPi	0/24	24/26 (92.8%)	<0.001 **
OS 12 months (death)	41%	15%	

What next?

1. What to do with the other 50% that are HR competent EOC?

-Can functional HRD phenotype be induced (HR inhibition)

- Imatinib/ Pi3K /HDAC/ HSP90 inhibitor
- **Hyperthermia**

2. Does HR status alter its microenvironment too to benefit survival?

- HR competent tumours will have increased mesenchymal phenotype/ inflammation-fibrosis/ / immune escape which can affect surgical resectability

What does heat do

Whole body hyperthermia or local heat

Heat sensitive vs Heat resistant cells

39 or 42 degrees Temperature range or heat

HSP90/HSP70

HSP70/90

ROS

Immune activation

DDR- HR/NER/Others

Mechanical

Rationale for targeted HIPEC (Hyperthermic Intraperitoneal Chemotherapy)

- Morbidity/ cost **Recent RCT**: improves survival
- Heat at 39-40 degree- immune/ inflammation axis
- Heat at 42 degree- compromise DNA repair

- **Pilot pre-clinical data: Heat sensitizes BRCA proficient HRC cell lines to PARPi, BRCA2 is down regulated-** **Mukhopadhyay et al, AACR DNA repair, 2016**

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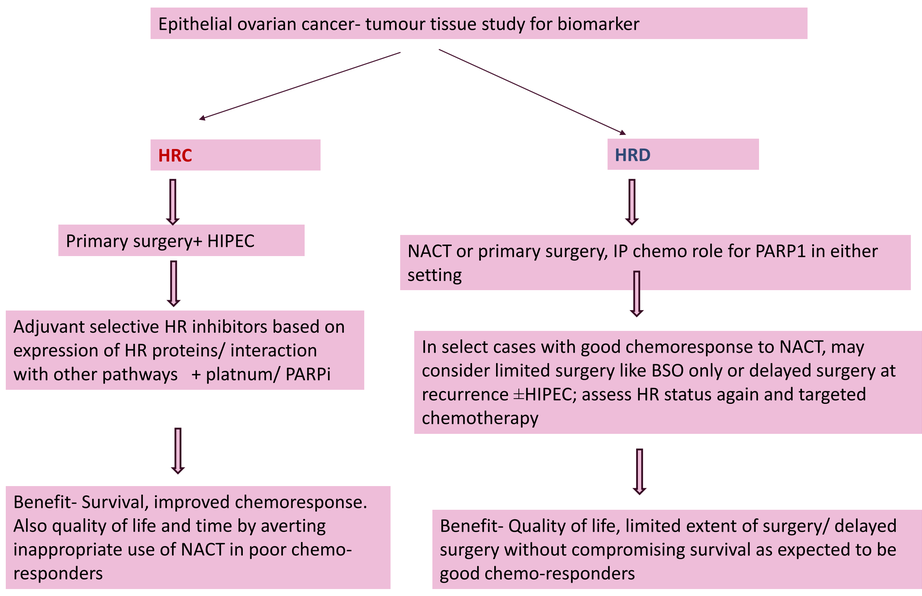
Research questions:

- **Is heat beneficial over and above IP chemo**
- **? Immune escape mechanism is different between HRC and HRD- Is there differential response to heat affecting different micro-environment?**
- **Personalised therapy/surgery using different approaches for HRC and HRD**



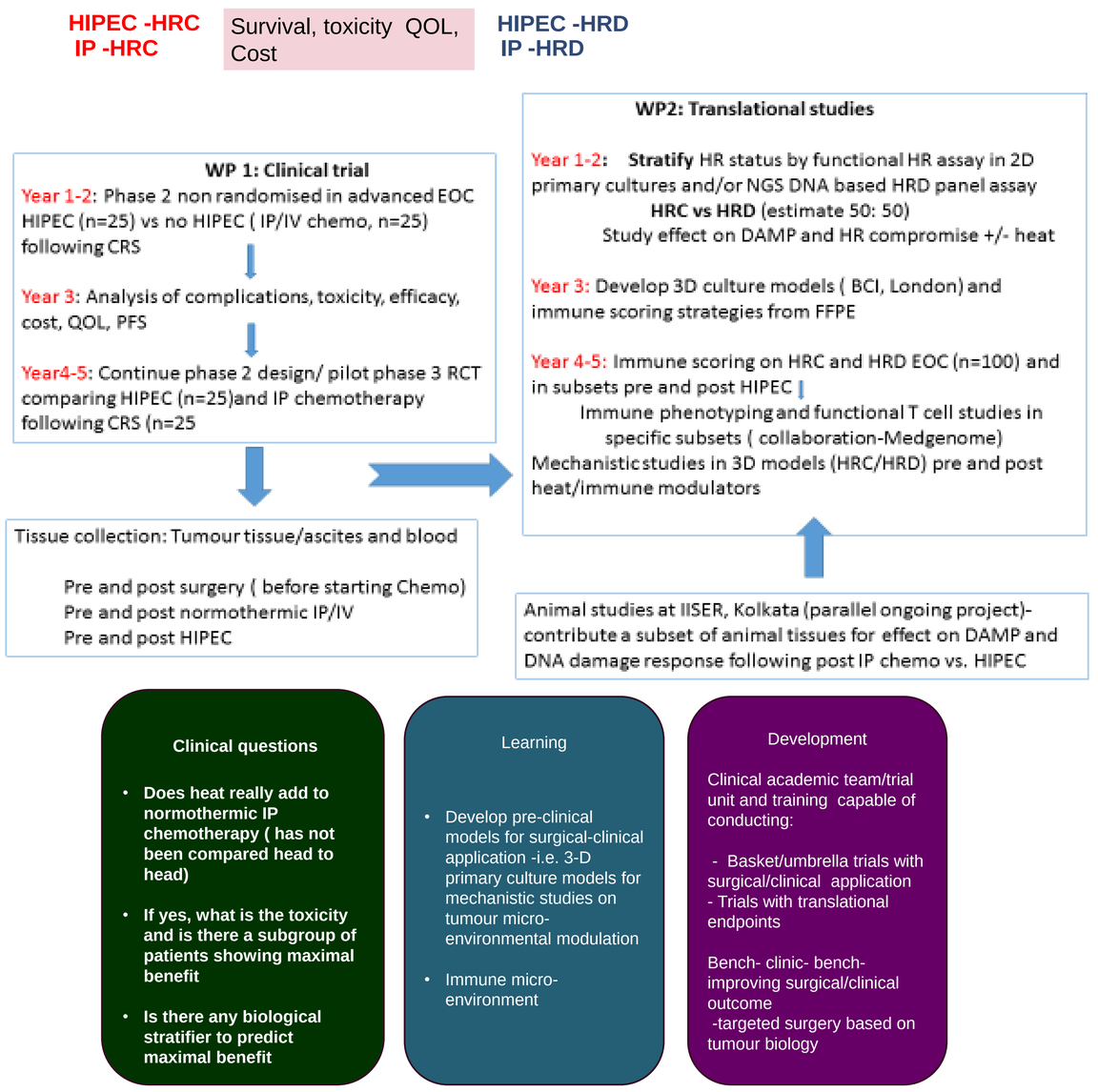
Experimental Plan:

1.Clinical study-

To assess feasibility and toxicity of HIPEC versus standard IP/systemic chemo after surgery

2. Translational-

To assess the effect of hyperthermia/HIPEC on DNA damage response and immune escape mechanism in HRC versus HRD EOC



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