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CONTRACTING ORGANIZATION: UNIVERSITÄT BERN

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14. ABSTRACT

Various inhibitors of poly(ADP-ribose) (PAR) polymerase (PARPi) have recently entered the clinic for the treatment of patients with ovarian cancers defective in homology-directed DNA repair, e.g. due to the loss of BRCA1/2 function. Despite the success of this approved novel therapy, drug resistance is a major clinical hurdle. The overall goal of this project is to target PARPi resistance in BRCA1/2-mutated high-grade serous ovarian cancer (HGS-OvCa), in order to optimize the use of PARPi and to develop new therapeutic approaches to overcome drug resistance.

To achieve this goal, we have addressed the following two specific aims in the first year of this project:
1. Targeting primary resistance by combining RNA-SCS-based tumor cell deconvolution with computational pathology and patient-derived organoids.
2. Targeting secondary resistance using LCM-guided whole exome sequencing and RNAseq of tumor samples collected from PARPi-resistant BRCA1/2-mutated HGS-OvCa samples.

In this technical report, we show that we have addressed all major tasks according to our initial plan. There are no major deviations, and we plan to publish our first data from this project in the coming reporting period. Importantly, with the loss of H2AX we present a novel mechanism that may indeed contribute to PARPi resistance in human ovarian cancer.

15. SUBJECT TERMS

high-grade serous ovarian carcinoma, BRCA1, BRCA2, poly(ADP-ribose) (PAR) polymerase inhibitors (PARPi), drug resistance, single cell RNA sequencing, digital pathology, 3D organoids

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TABLE OF CONTENTS

1. INTRODUCTION:

Various inhibitors of poly(ADP-ribose) (PAR) polymerase (PARPi) have recently entered the clinic for the treatment of patients with ovarian cancers defective in homology-directed DNA repair, *e.g.* due to the loss of BRCA1/2 function. Despite the success of this approved novel therapy, drug resistance is a major clinical hurdle. The overall goal of this project is to target PARPi resistance in *BRCA1/2*-mutated high-grade serous ovarian cancer (HGS-OvCa), in order to optimize the use of PARPi and to develop new therapeutic approaches to overcome drug resistance.

2. KEYWORDS:

high-grade serous ovarian carcinoma, BRCA1, BRCA2, poly(ADP-ribose) (PAR) polymerase inhibitors (PARPi), drug resistance, single cell RNA sequencing, digital pathology, 3D organoids

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim 1: Targeting primary resistance by combining RNA-SCS-based tumor cell deconvolution with computational pathology and HGS-OvCa PDOs	**Site 1**	**Site 2**	**Completion status**
Major Task 1: Classification of HGS-OvCa patients using single cell sequencing of selected patients followed by bulk RNAseq of FFPE material			
Subtask 1- Human Research Protection Office (HRPO) approval	X	X	Planned: Sep 22 Actual: Sep 22
Subtask 2- Update of reference profiles from the various cellular components present in HGS-OvCa using already available single cell RNA sequencing data of five patients with BRCA1/2 mutations	X		Planned: Sep 22 Actual: Sep 22
Subtask 3- Applying the tumor cell deconvolution to the bulk RNAseq data of >800 ovarian cancer patients	X		Planned: Dec 22 Actual: April 23
Subtask 4- Correlating tumor cell deconvolution data with clinical data	X		Planned: Feb 23 Actual: June 23
Milestone 1 – Classification of HGS-OvCa patients using single cell sequencing of selected patients followed by bulk RNAseq of FFPE material – achieved	X		Planned: March 23 Actual: June 23

Major Task 2: An artificial intelligence-based algorithm to detect ovarian cancers with a mutation in the BRCA1/2 DNA-BD			
Subtask 1- Computational pathology of the tumor-stroma ratio using already digitalized whole slide images of > 800 randomly chosen ovarian cancer patients from the PAOLA trial	X		Planned: April 23 Actual: Aug 23
Subtask 2- Computational pathology of tumor-infiltrating lymphocytes using already digitalized whole slide images of > 800 randomly chosen ovarian cancer patients from the PAOLA trial	X		Planned: May 23 Actual: August 23
Subtask 3- Computational pathology of secondary lymphatic structures using already digitalized whole slide images of > 800 randomly chosen ovarian cancer patients from the PAOLA trial	X		Planned: Aug 23 Actual: Aug 23
Milestone 2 – An artificial intelligence-based algorithm to detect ovarian cancers with a mutation in the BRCA1/2 DNA-BD – achieved	X		Planned: March 24 Actual: 50%
Major Task 3: Functional validation of the increased sensitivity of tumors with a mutation in the BRCA2 DNA-BD using HGS-OvCa PDOs			
Subtask 1- Human Research Protection Office (HRPO) approval		X	Planned: Sep 22 Actual: Sep 22
Subtask 2- Biobanking of BRCA1/2-mutated HGS-OvCa PDOs and their genetic characterization (e.g., *BRCA1/2* mutational status)		X	Planned: Aug 23 Actual: Aug 23
Subtask 3- Optimizing technical conditions for lentiviral transductions of 3D organoids	X		Planned: Aug 23 Actual: Aug 23
Subtask 6- Support of 3D cell culture and lentivirus production	X		Planned: Feb 25 Actual: 30%
Milestone 3 – Functional validation of the increased sensitivity of tumors with a mutation in the BRCA2 DNA-BD using HGS-OvCa PDOs – achieved	X	X	Planned: Feb 25 Actual: 30%
Specific Aim 2: Targeting secondary resistance using LCM-guided whole exome sequencing and RNAseq of tumor samples collected from PARPi-resistant BRCA1/2-mutated HGS-OvCa samples	**Site 1**	**Site 2**	**Completion status**
Major Task 4: Validation of mechanisms of secondary PARPi resistance identified in preclinical model systems in PARPi-resistant BRCA1/2-mutated HGS-OvCa samples.			

Subtask 1- IRB approval		X	Planned: June 22 Actual: July 22
Subtask 2- Human Research Protection Office (HRPO) approval		X	Planned: Dec 22 Actual: 50%
Subtask 3- Biobank of tumor samples collected from BRCA1/2-mutated HGS-OvCa that became resistant to PARP inhibitors		X	Planned: Aug 26 Actual: 10%
Subtask 4- Contact of the investigating centers to seek for the number of cases/biopsies available in each center		X	Planned: Dec 22 Actual: 50%
Subtask 5- Obtain informed consent and collect tumor samples and clinical data of the patients included in the study		X	Planned: Dec 23 Actual: 10%
Subtask 6- Generation of a biobank of formalin-fixed paraffin-embedded (FFPE) tumor samples collected from 50 HGS-OvCa with BRCA mutations (germline or somatic) who became resistant to PARPi		X	Planned: Dec 23 Actual: 10%
Subtask 7- Laser-capture microdissection of cancer cells and extract RNA/DNA from microdissected tissues		X	Planned: Feb 24 Actual: 10%
Milestone 4 – Validation of mechanisms of secondary PARPi resistance identified in preclinical model systems in PARPi-resistant BRCA1/2-mutated HGS-OvCa samples – achieved		X	Planned: June 25 Actual: 50%

What was accomplished under these goals?

1) Major activities
   In the first year of this project, we focused our activities on specific aim 1, *i.e.,* combining RNA-SCS-based tumor cell deconvolution with computational pathology and HGS-OvCa PDOs. Moreover, we started to address specific aim 2*, i.e.,* targeting secondary resistance using LCM-guided whole exome sequencing and RNAseq of tumor samples.

2) Specific objectives:
   For specific aim 1, we worked on the following specific objectives:
   - Single cell sequencing of HGS-OvCa followed by bulk RNAseq (Major Task 1)
   - Development of an artificial intelligence-based algorithm to detect ovarian cancers with a mutation in the BRCA1/2 DNA-BD (Major Task 2)
   - Functional validation of the increased sensitivity of tumors with a mutation in the BRCA2 DNA-BD using patient-derived organoids from ovarian cancer (Major Task 3)

   For specific aim 2, we started to validate mechanisms of secondary PARPi resistance using BRCA1/2-mutated ovarian cancer samples (Major Task 4).

3) Significant results or key outcomes:

Major Task 1:

We used a deconvolution-based approach to estimate the proportions of different cell type populations based on bulk mRNA sequencing data of the ovarian cancer samples, complemented by differential gene expression analysis and histopathological assessment to identify predictive signatures. We identified and subsequently validated distinct microenvironments containing specific populations of immune and epithelial cells that differentiate treatment benefit. Our preliminary data are presented below in **Fig. 1**. These data, including further follow-up validations are in preparation for a publication in 2024.

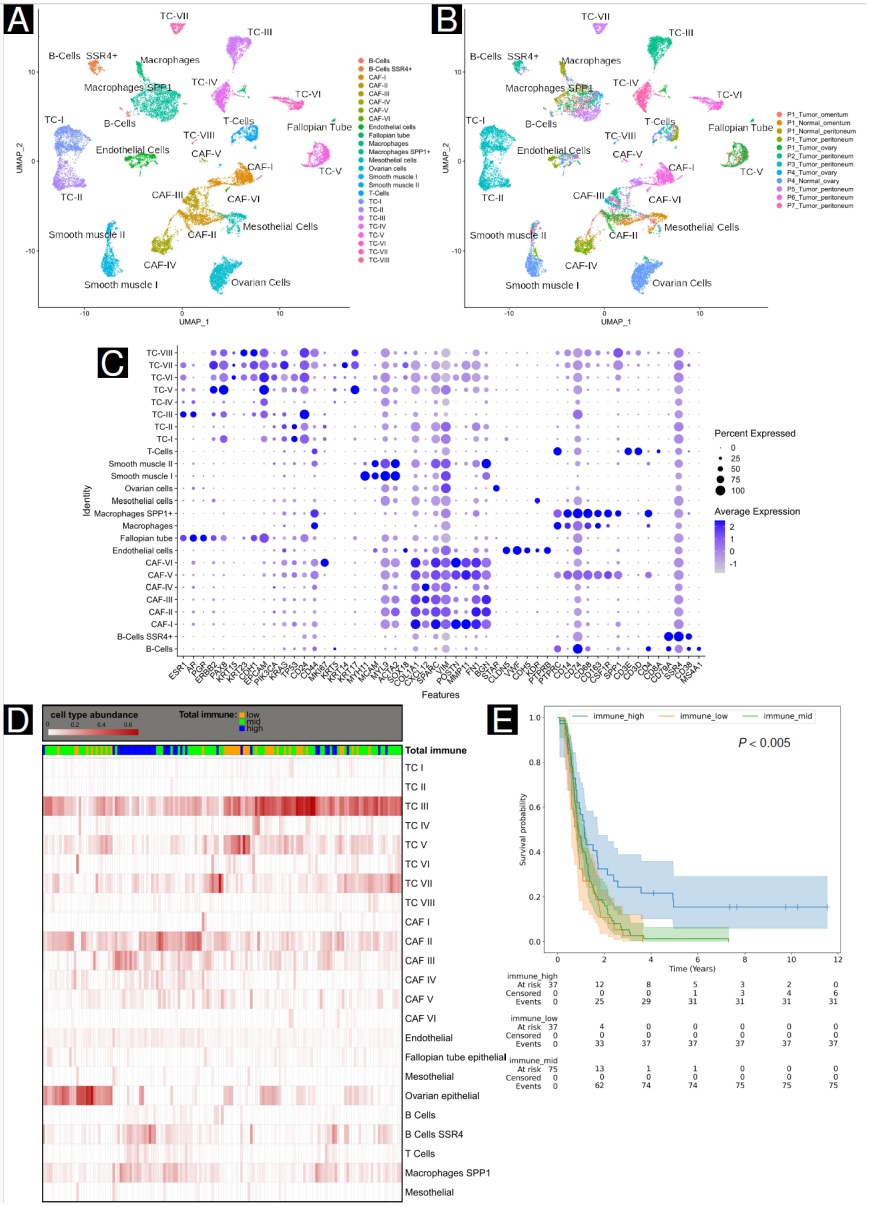

Figure 1. Single cell deconvolution for calculating patient cell type abundances from single cells expression reference profiles. *A) UMAP projection of single cells based on their normalized expression counts. Cells with similar expression profiles are proximally located, allowing for clustering, and annotating single cells according to their respective cell type. B) Annotating the UMAP projection based on sample origin shows separation. C) Differential expression between annotated cell type clusters and selected marker genes shows. D) Heatmap showing cell type abundances as estimated by single cell deconvolution for every patient. Hierarchical clustering of patients shows a heterogeneous landscape of cell type composition, with varying degrees of immune infiltration. E) Kaplan Meier Curve using quartile cut-offs, shows a significant association of estimated immune cell abundance with progression free survival (P<0.005).*

Major Task 2:

The increasing digitization of routine clinical histology slides into whole slide images (WSI) has spurred great interest in the development of WSI-based biomarkers for diagnosis, prognosis, and therapy response. These biomarkers are typically based on patterns associated with the location and type of individual histologic objects. While current hardware and machine learning algorithms can locate and type objects at scale, the manual assignment and review of large labeled datasets used to train or validate models remains arduous. Appreciating the need for an open-source force multiplier for labeling histological objects, we developed PatchSorter (PS). PS is a user-friendly, browser-based tool, which allows the user to leverage deep learning (DL) to quickly review and apply labels at a group, as opposed to a single object, level (**Fig. 2**). We demonstrated that this "bulk" labeling approach improves labeling efficiency across four use cases, spanning three levels of increasing object complexity. A manuscript describing this novel algorithm is in preparation for publication.

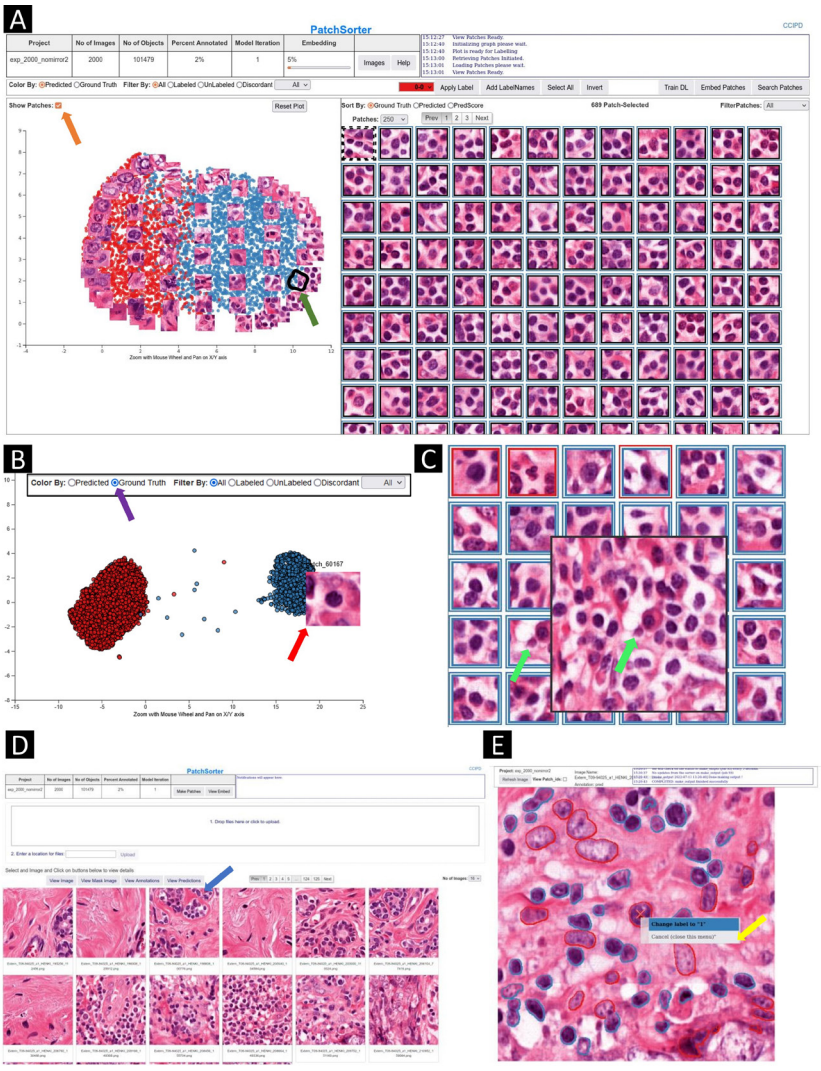

Figure 2. PatchSorter user interface. *(A) The embedding plot after initial embedding (left) with corresponding grid plot (right). The two-dimensional embedding plot places patches with the same deep learned features in close proximity, causing objects with the same object class to cluster. The user lassos points (black contour with green arrow) which then appear in the grid plot for labeling using efficient keyboard shortcuts. In the embedding plot, a subset of patches can be overlaid to aid in selecting regions in the embedding space (orange arrow). (B) The embedding plot allows for coloring patches by prediction and ground truth (purple arrow). The embedding plot shows the same data set as (A) after eight model iterations where the embedding space is well separated by ground truth labels. Hovering over a point in the embedding space shows the corresponding patch (red arrow). (C) Grid plot coloring shows current predictions and ground truth. The inner square color represents ground truth while the outer square color represents model prediction, with black indicating that the patch is not yet labeled. Right-clicking on patch in the grid plot shows a larger region of interest (ROI) for context (green arrows). (D) From the image pane, prediction and ground truth labels can be visualized (blue arrow) in the output reviewer. (E) Here, objects labels can be updated via a right click on the object (yellow arrow)*

Using PS for labeling histological features in ovarian cancer, we are working on developing an AI-based algorithm to identify specific features of ovarian cancers with a mutation in the BRCA1/2 DNA-BD. Thus far, these analyses have not yielded a reliable signature. In year 2 of the project we

will continue these efforts by investigated tumor-cell intrinsic patterns (Subtask 4) and merging the above-mentioned computational pathology analyses with the RNAseq analysis (subtask 5). Moreover, we shall overlay our machine learning with histologic slides of mouse tumors with defined BRCA1 or BRCA2 mutations.

Major Task 3:
We successfully biobanked the indicated BRCA1/2-mutated patient-derived organoids and optimized conditions for lentiviral transductions.
The subject protocol was approved by the cantonal (Geneva) Research Ethics Commission (CCER) on 20 September 2022. The U.S. Army Medical Research and Development Command (USAMRDC), Office of Human and Animal Research Oversight (OHARO), Office of Human Research Oversight (OHRO) reviewed the protocol and found that it complies with applicable DOD, U.S. Army, and USAMRDC human subject's protection requirements.
We then established PDO generated from HGS-OvCa fresh samples that have been characterized for their sensitivity to PARPi (**Fig. 3**).

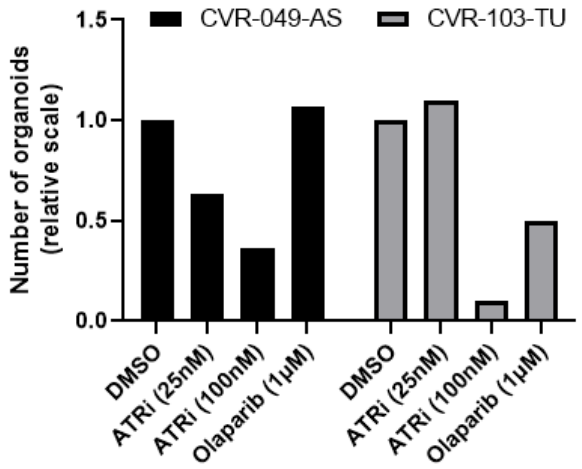

Figure 3: PDO sensitivity to PARPi reflects patient response. *CVR-049-AS is derived from a patient that showed resistance to PARPi but partial sensitivity to ATR inhibition. CVR-103-TU is derived from a patient that is partially sensitive to PARPi and extremely sensitive to ATRi.*

DNA has been extracted from PDO lines already established and sent for genomic characterization using SNP arrays, to confirm their homologous recombination (HR) deficiency status. For the *BRCA*-mutated PDO, we will sequence the DNA in reporting period 2 to confirm the preservation of the *BRCA* mutations.

Major Task 4:
We collected paired biopsies from 5 patients with *BRCA1/2*-mutated HGS-OvCa enrolled in the CHIOVAR study approved by HRPO, 4 with germline mutations of *BRCA1* and 1 with a somatic mutation of *BRCA2* (**Table 2**).

CHIOVAR	mutation	BRCA mutation
CHIOVAR59	BRCA2 (somatic)	c.3376G>T/p.Glu1126Ter
CHIOVAR77	BRCA1 (germline)	c.181T>G/p.Cys61Gly
CHIOVAR113	BRCA1 (germline)	c.181T>G/p.Cys61Gly

CHIOVAR100	BRCA1 (germline)	c.367del/p.Ser123LeufsX40
CHIOVAR132	BRCA1 (germline)	c.3331_3334del/p.Gln1111AsnfsX5

Table 1: list of BRCA mutation of paired biopsies collected

By studying resistance to poly(ADP-ribose) polymerase (PARP) inhibitors in our BRCA1/2-deficient preclinical model systems, we identified a hitherto unknown function of H2AX in replication fork biology. We observed that phosphorylated histone H2AX promotes replication fork degradation in BRCA1/2-deficient cells, by counteracting CtIP-mediated fork protection. As a result, H2AX loss restores replication fork stability and increases chemoresistance in BRCA1/2-deficient tumor cells without restoring homology-directed DNA repair, as highlighted by the lack of DNA damage-induced RAD51 foci. Hence, our results demonstrate a novel role for H2AX in replication fork biology and establish a function of H2AX separable from its classical role in DNA damage signaling and double-strand repair. To validate these findings using ovarian cancer samples taken before and after chemotherapy, we are currently analyzing H2AX expression using immunohistochemistry. Since we have a clear target and a working antibody, we decided that this would be more straight-forward than LCM-based RNA analysis for this target. We established the protocols for the staining and indeed we see a lack of expression in some of the therapy-resistant ovarian cancers. **Fig. 4** depicts an example of CHIOVAR59, a drug-resistant *BRCA2*-mutated tumor. These protocols are now applied in reporting period 2 to test at least 10 matched samples collected from individual patients before and after chemotherapy. We are planning to include these data in a manuscript on the role of H2AX in facilitating PARPi-induced sensitivity in the next reporting period. Moreover, we will apply this protocol to our entire collection of 50 matched tumor samples, once the sampling has been completed.

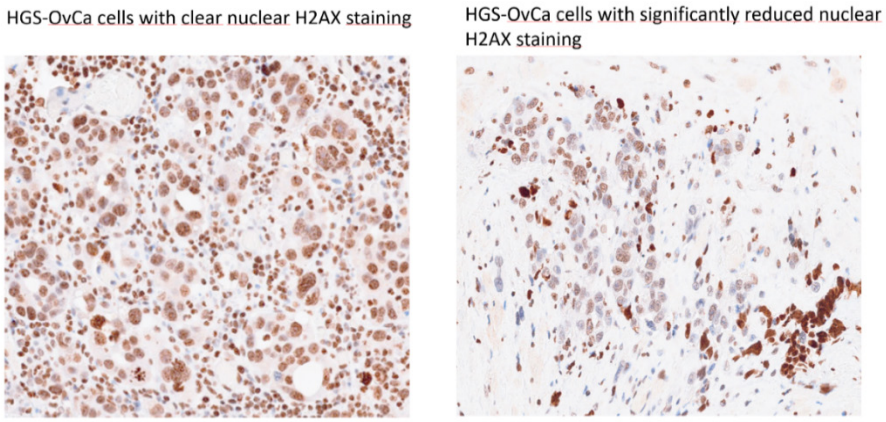

Figure 4. *Examples of the immunohistochemical analysis of nuclear H2AX expression (brown) in drug-resistant BRCA2-mutated ovarian cancer (CHIOVAR59). Left panel shows an example where we found clear expression in the cell nucleus, whereas on the right panel there is a clear depletion of H2AX in the majority of the tumor cells.*

4) Other achievements

As an innovative tool to address Major Task 4, we also established the use of spatial transcriptomics (ST) using the Visium platform of 10x Genomics in the Rottenberg laboratory. Dissecting tissue compartments in ST remains challenging due to limited spatial resolution and dependence on single-cell reference data. We therefore developed Chrysalis, a novel method to rapidly detect tissue compartments through spatially variable gene (SVG) detection and archetypal analysis without external references. We applied Chrysalis on ST datasets originating from various species, tissues and technologies and demonstrated state-of-the-art performance in identifying cellular niches (**Fig. 5**).

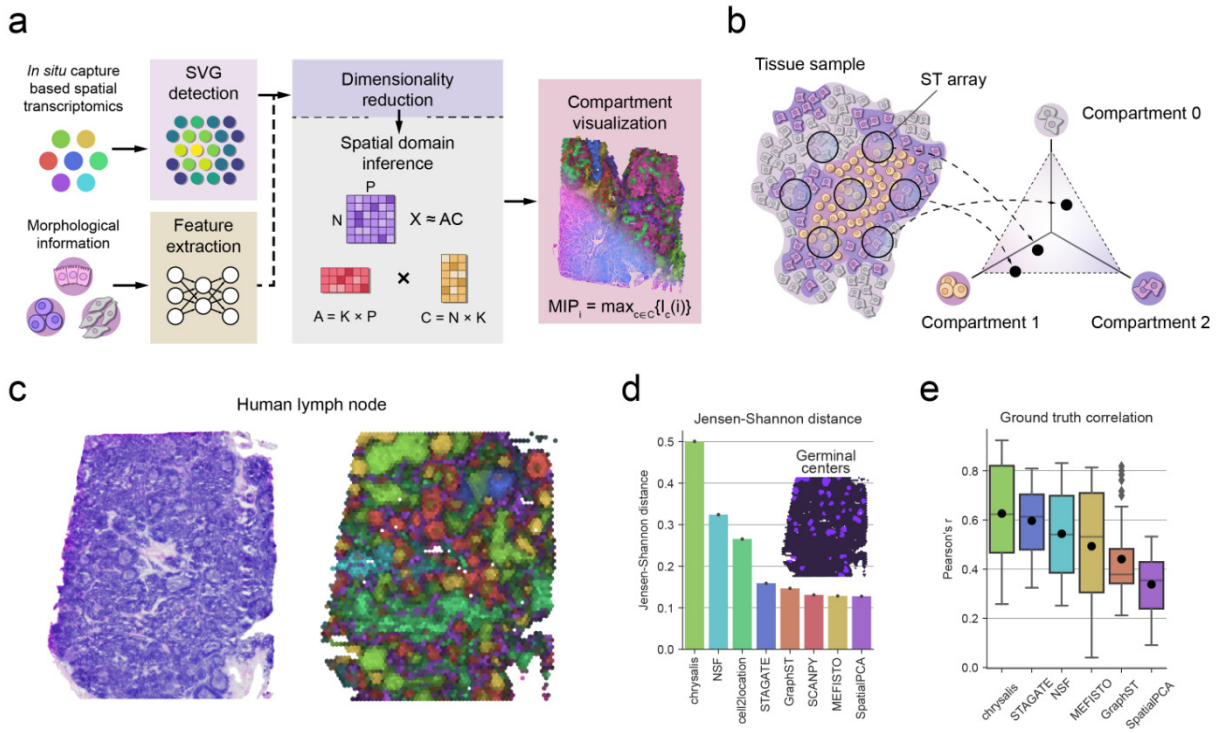

Figure 5. Chrysalis enables accurate tissue compartment identification in the human lymph node. a, *Chrysalis workflow begins by selecting SVGs from the gene expression matrix to construct a low-dimensional representation of ST data using dimensionality reduction. This can be augmented by integrating morphological feature vectors extracted from the corresponding H&E image tiles. After dimensionality reduction, the integrated low-dimensional feature space is used to find spatial domains distinct in gene expression and, if available, morphology as well. By leveraging archetypal analysis, the original feature matrix X is decomposed into two matrices, A and C, where C contains the tissue compartment score for each observation, and A stores the contributions of the basis vectors for the tissue compartments. A can be used to reconstruct the weights of individual SVGs for K compartments. Finally, Chrysalis uses a maximum intensity projection-based visualization to project C to the tissue space.* ***b,*** *Chrysalis finds discrete tissue compartments that appear as vertex points of a multi-dimensional simplex fitted to the low-dimensional feature space. These correspond to capture spots exclusively covered by one distinct cellular microenvironment, and every other capture spot containing the mixture of these compartments is represented as a linear combination of them.* ***c,*** *Human lymph node H&E image (left panel) and the projection of the tissue compartments identified by Chrysalis (right panel).* ***d,*** *Jensen-Shannon distance of domain score distributions in the germinal center annotations (inset) and the rest of the sample across the applied methods.* ***e,*** *Boxplots of Pearson's r values calculated between the 34 reference cell type abundances inferred with cell2location and the domain scores for the six methods applied to the lymph node dataset (center line: median, box limits: upper and lower quartiles, whiskers: 1.5x interquartile range, diamonds: outliers, black dot: average value).*

Hence, we generated another algorithm for the state-of-the-art analysis of ST data that we may apply to selected ovarian cancer samples. As a complementary tool to LCM-based DNA/RNA sequencing, ST allows us to directly overlay molecular analyses with morphologic data.

In summary, we have addressed all of the tasks we outlined for the first project year, and we successfully achieved Milestone 1 (related to Major Task 1) – *Classification of HGS-OvCa patients using single cell sequencing of selected patients followed by bulk RNAseq of FFPE material*. We expect to publish our first data from this project in year 2.

Regarding Milestone 2 (related to Major Task 2)– *An artificial intelligence-based algorithm to detect ovarian cancers with a mutation in the BRCA1/2 DNA-BD*, we will continue our efforts of developing such an algorithm as planned in reporting period 2.

With H2AX, we already have a highly promising candidate for successful validation for Milestone 4 (related to Major Task 4) - *Validation of mechanisms of secondary PARPi resistance identified in preclinical model systems in PARPi-resistant BRCA1/2-mutated HGS-OvCa samples*. Achieving milestone 4 was planned for month 34, and we are optimistic that loss of H2AX will already be validated in the second year of the project.

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

In the next reporting period, we aim to publish the data presented above. We may also present these at international conferences (*e.g.,* at the annual AACR conference in April 2024). In addition, we will continue our efforts to complete the Major Tasks 2, 3 and 4 and successfully achieve Milestones 2, 3 and 4

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report, as additional validations are ongoing. If loss of H2AX can indeed be confirmed as the mechanism of PARPi resistance in patients, this would be a major breakthrough. We expect the confirmation of these data in the next reporting period.

What was the impact on other disciplines?

The PatchSorter and Chrysalis algorithms that were developed for this project are highly valuable for the analysis of other tumor entities, in addition to ovarian cancer.

What was the impact on technology transfer?

We plan to make our algorithms available to the public through open access in the next reporting period.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

In Major Task 4 there will be two biobanks to collect paired biopsies from 50 patients. The first biobank (CHIOVAR study) supervised by site 2 was approved by local IRB and HRPO and paired biopsies from 5 patients were collected. For the second biobank (PARP-RES) that will be supervised by the collaborating site in France, we had a few months delay with the contract of collaboration between site 2 and the collaborating site. The contract of collaboration and Material-Transfer Agreement have now been signed, the research protocol of PARP-RES has been approved by the local IRB and will be submitted in October 2023 to HRPO. This will delay the completion of subtasks 2 and 4 of Major Task 4 until project month 15. This delay does not affect the completion of Milestone 4 planned for June 2025, because we have already established the necessary protocols with the available material from the CHIOVAR study.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

Nothing to report.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers and presentations.

Nothing to report.

- **Website(s) or other Internet site(s)**

  Nothing to report.

- **Technologies or techniques**

  With PatchSorter and Chrysalis we developed two algorithms that are useful digital pathology and spatial transcriptomics analyses.

- **Inventions, patent applications, and/or licenses**

  Nothing to report.

- **Other Products**

  Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Sven Rottenberg*
Project Role:	*Principal investigator*
Researcher Identifier:	*ORCID: 0000-0003-2044-9844*
Nearest person month worked:	*2.4*
Contribution to Project:	*Supervising the project at site 1.*
Funding Support:	*No*

Name:	*Intidhar Labidi-Galy*

Project Role:	*Principal investigator*
Researcher Identifier:	*ORCID: 0000-0002-0824-3475*
Nearest person month worked:	*2*
Contribution to Project:	*Supervising the project at site 2.*
Funding Support:	*No*

Name:	*Cédric Walker*
Project Role:	*PhD student, site 1*
Researcher Identifier:	
Nearest person month worked:	*12*
Contribution to Project:	*Addressing Major Tasks 1+2*
Funding Support:	*Yes*

Name:	*Kerry Woods*
Project Role:	*staff scientist, site 1*
Researcher Identifier:	*ORCID: 0000-0002-0445-9797*
Nearest person month worked:	*2*
Contribution to Project:	*Optimizing the technical conditions for lentiviral transductions of 3D organoids (Major Task 3)*
Funding Support:	*No*

Name:	*Denise Howald*
Project Role:	*Laboratory Technician, site 1*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*2*
Contribution to Project:	*Support of 3D cell culture and lentivirus production (Major Task 3)*
Funding Support:	*No*

Name:	*Valentine Du Bois*
Project Role:	*Staff scientist*
Researcher Identifier:	
Nearest person month worked:	*3*
Contribution to Project:	*Addressing Major Task 3 (Biobanking of BRCA1/2-mutated HGS-OvCa PDOs and their genetic characterization, (e.g., BRCA1/2 mutational status)*
Funding Support:	*No*

Name:	*Aliaksandra Kakoichankava*
Project Role:	*PhD student, site 2*
Researcher Identifier:	
Nearest person month worked:	*4*
Contribution to Project:	*Addressing Major Task 4 (Validation of mechanisms of secondary resistance to PARPi identified in preclinical*

	model systems in PARPi-resistant BRCA1/2-mutated HGS-OvCa samples)
Funding Support:	*Yes*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

Nothing to report.

9. APPENDICES:

Nothing to report.