**Personally Suited Oncology - Grant Proposal**

**Clinical Implications of Sub-grouping *MDM2* Positive Tumors by Amplicon Structure and Co-amplified Genes**

**Participant Roles:**

Principle Investigator – Dr Aviad Zick

**Institution**

Hebrew University - Sharett Institute for Oncology, Hadassah Medical Center

**Introduction –** *MDM2* encodes MDM2, a protein that binds P53 acidic activation domain leading to the loss of P53 transcriptional activity1. P53 induces *MDM2* transcription thus a P53 activity auro-regulatory negative feedback loop is formed2. Adipose tissue tumors (ATT) are a diverse clinical entity spanning from slowly growing local tumors to aggressive metastatic disease3. Ring chromosomes and long marker chromosomes containing multiple copies of the chromosome 12 q13-q15 region characterize ATT4. The recurrent amplified are of chromosome 12 q15 region contains the *MDM2*, *CPM*, and *SLC35E3* genes5. *MDM2* amplification, defined as multiple copies of a DNA segment containing the *MDM2* gene6 is correlated with *MDM2* overexpression7.

Three principal amplicon structures were described in tumor amplified DNA: inverted duplication (ID), tandem repeat (TR) and double minute (DM)8. In ID one DNA segment is connected to the same segment in an inverted orientation, telomeric end to telomeric end and centromeric end to centromeric end. In TR, a DNA segment is connected to the same segment as a tandem repeat, the telomeric end of one segment is linked to the centromeric end of a second segment. A DM is composed of several DNA segments from different parts of the genome that are oriented randomly. A DM can be found either as an extra-chromosomal DNA fragment or as part of a chromosome9. An *MDM2* amplicon with an DM was described in a glioblastoma multiform xenograph10 and a well differentiated sarcoma patient11. *MDM2* amplification in 80% liposarcoma is found as a large complex structures called Tyfonas12.

Identification of *MDM2* amplification is performed using fluorescence in situ hybridization (FISH)4, and immunohistochemistry (IHC) for MDM2 overexpression13. These methods are the gold standard and are routinely used in clinical care. Further characterization of DNA amplification can be performed using digital droplet PCR (ddPCR) and low coverage whole genome sequencing (lcWGS). DdPCR is a robust and precise method for enumerating the copy number (CN) of a specific DNA segment14. LcWGS identifies DNA amplifications and deletions throughout the genome as well as amplicon structure (AS)15 but also suffers from bias in CN enumeration due to variable efficacy in library preparation and DNA sequencing in different parts of the genome16, combining these methods can detail an amplicon CN and AS. By applying this approach to *ERBB2* amplified tumors we were able differentiates between local and advanced tumors, determine if a tumor is a recurrent tumor or second primary tumor and identify amplified oncogenes that may serve as targets for therapy17.

In this work, we attempt to investigate the clinical impact of *MDM2* amplicon characterization in ATT, based on AS and co-amplified genes using ddPCR and lcWGS.

**Research plan –**

In this pilot retrospective study we intended to test 60 samples of *MDM2* positive ATT. The samples *MDM2* copy number, amplicon structure, number of segments and size will be correlated to clinical variables such as age, sex, tumor site, pathology, stage, response to treatment and overall survival.

**Part 1** – Patients suffering from Sarcoma that previously signed an informed consent Form for Participation in Whole-Genome Genetic Study (0346-12-HMO) are candidates for this trial.

**Part 2** – Sarcoma samples are tested for *MDM2* amplification using ddPCR, positive samples are samples with six or more copies.

**Part 3** – *MDM2* positive sarcomas are lcWGS and analyzed using FAST, a program we developed17 for identifying amplicon size, structure and co-amplified genes.

**Part 4** – *MDM2* amplicon size, structure and co-amplified genes is correlated to clinical features including age, sex, tumor site, pathology, stage, response to treatment and overall survival.

**Preliminary results -**

**Patient characteristics -** Table 1 reports the characteristics of 30 patients suffering from sarcoma, one is a known *TP53* carrier and one suffers from Tuberous sclerosis.

***MDM2* copy number differentiates between non-myxoid liposarcomas and other sarcomas -** We performed ddPCR to quantify *MDM2* CN on sarcoma samples. We found that in the non-myxoid liposarcomas, 11 of 12 samples were positive and in addition, one high-grade sarcoma is positive. *MDM2* gene is not amplified in 18 sarcomas of other pathologies, in lipomas and one dedifferentiated liposarcoma with high and low grade component, a rhabdomyosarcomatous differentiation and a dedifferentiated liposarcoma, fisher exact test statistic value is < 0.00001 (figure 1).

**The AS of *MDM2* amplicons is diverse in liposarcoma -** Preliminary results of 8 liposarcomas and one high grade sarcoma analyzing using lcWGS show a diverse pattern. *MDM2* copy number ranging from 6-16, amplicon structure of either inverted duplication or double minute composed of 1-31 segments with a sizes ranging from 0.6-22.6 MB (figure 2). The *AIM2*, *CADM3*, *ATF6*, *CDK4*, *PBX1*, *NOTCH2* and *RXRG* are co-amplified in some of the tumor samples (figure 3). This diversity may be part of the different clinical aspects of liposarcomas.

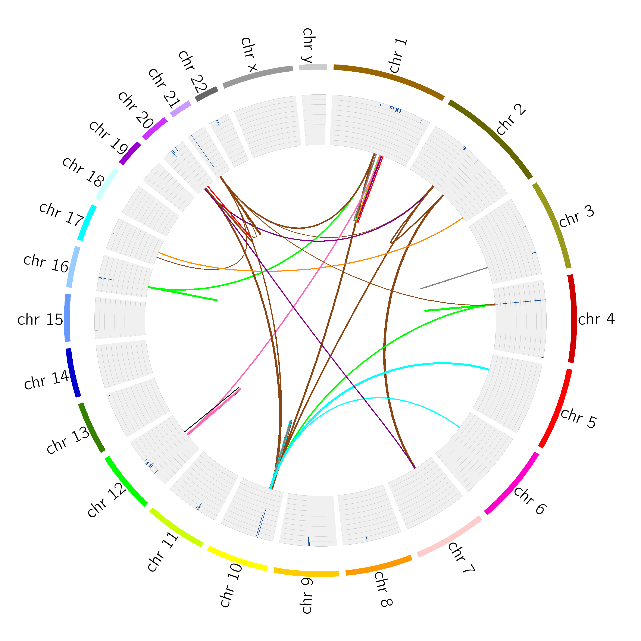
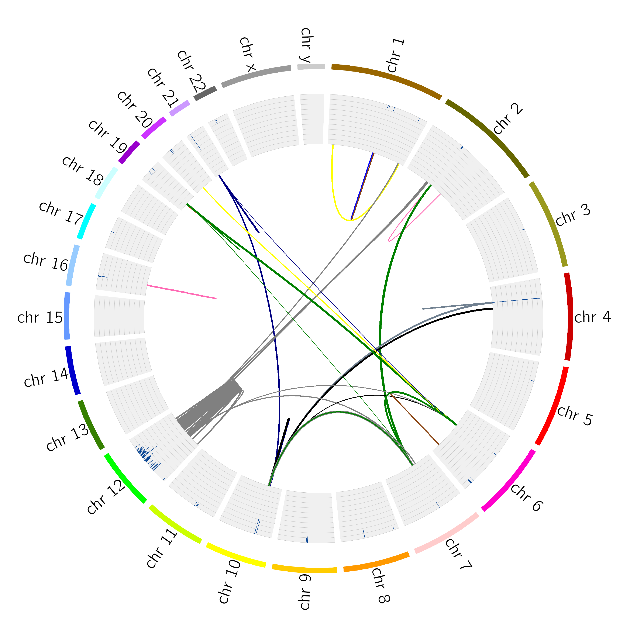
*MDM2* copy number

Non myxoid liposarcoma

Sarcoma and benign lipoma

Figure 1 – *MDM2* copy number in study samples.

We measured *MDM2* CN using ddPCR in 13 samples derived from non myxoid liposarcoma, colored red and 19 sarcomas of other pathologies and benign lipomas colored blue. 13 tumors were found ddPCR positive, using a cut-off of six copies, and were further examined using lcWGS.



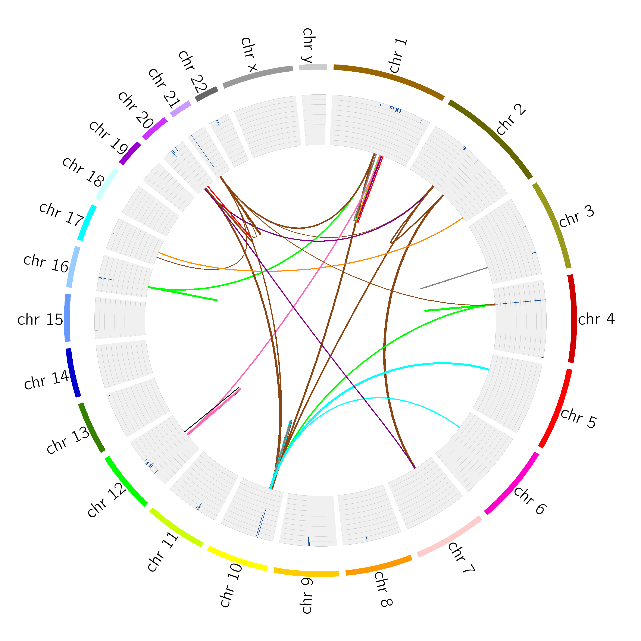
*MDM2*

*MDM2*

SRC14 SRC20

Figure 2 – *MDM2* amplicon structure is different in patients with liposarcoma.

FAST analysis of low coverage whole genome sequencing (lcWGS) of two dedifferentiated liposarcoma visualized using Circus. The external ring represents chromosomal location; the inner ring shows areas of amplification as blue bars. Colored lines represent structural variations (SV), all the SV in an amplicon are colored with the same color. Both (SRC14 and P20) are dedifferentiated liposarcoma, SRC14 *MDM2* amplicon is a single segment size 0.9 MB with an ID structure (blue); SRC20 *MDM2* amplicon is a composed of 31 segments size 15.1 MB with an ID structure (gray).



*CDK4*

*CDK4*

*MDM2*

*MDM2*

SRC14

Figure 3 – *CDK4* co-amplification with *MDM2*.

FAST analysis of low coverage whole genome sequencing (lcWGS) of dedifferentiated liposarcoma is visualized using Circus. The external ring represents chromosomal location; the inner ring shows areas of amplification as blue bars. Colored lines represent structural variations (SV), all the SV in an amplicon are colored with the same color. In SRC14 *CDK4* co-amplification, colored pink is found.

Table 1 – Sarcoma patient characteristics

|  |  |
| --- | --- |
| **Median Age at Diagnosis (range)** | 60 (27-81) |
| **Patient gender** | N (%) |
| Female | 15 (50%) |
| Male | 15 (50%) |
| **Patient ethnicity** | N (%) |
| Ashkenazi Jew | 11 (37) |
| Sephardic Jew | 10 (33) |
| N/A | 9 (30) |
| **Primary tumor Site** | N (%) |
| Trunk and extremity | 19 (63) |
| Head and neck | 1 (3) |
| Visceral organs | 3 (10) |
| Retroperitoneal | 7 (23) |
| **Tumor Stage** | N (%) |
| 0 | 5 (17) |
| I | 9 (30) |
| II | 1 (3) |
| III | 6 (20) |
| IIIC-IV | 7 (23) |
| Recurrent | 2 (7) |
| **Tumor Pathology** | N (%) |
| benign | 7 (23) |
| Non myxoid liposarcoma | 15 (50) |
| Other sarcoma | 8 (27) |

**Bibliography**

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3. Robson, M. *et al.* Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation . *N. Engl. J. Med.* (2017) doi:10.1056/nejmoa1706450.

4. Struewing, J. P. *et al.* The Risk of Cancer Associated with Specific Mutations of BRCA1 and BRCA2 among Ashkenazi Jews . *N. Engl. J. Med.* (1997) doi:10.1056/nejm199705153362001.

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6. Zick, A. *et al.* A BRCA1 Frame Shift Mutation in Women of Kurdish Jewish Descent. *Open Breast Cancer J.* (2015) doi:10.2174/1876817220150529e001.

7. Sagi, M. *et al.* Two BRCA1/2 founder mutations in Jews of Sephardic origin. *Fam. Cancer* (2011) doi:10.1007/s10689-010-9395-9.

8. Silverman, B. & Keinan-Boker, L. Cancer in the arab population in Israel - current trends. https://www.health.gov.il/PublicationsFiles/CANCER\_ARB\_2017.pdf.

9. Bieging, K. T., Mello, S. S. & Attardi, L. D. Unravelling mechanisms of p53-mediated tumour suppression. *Nature Reviews Cancer* (2014) doi:10.1038/nrc3711.

10. Mai, P. L. *et al.* Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. *Cancer* (2016) doi:10.1002/cncr.30248.

11. Kratz, C. P. *et al.* Cancer screening recommendations for individuals with Li-Fraumeni syndrome. *Clin. Cancer Res.* (2017) doi:10.1158/1078-0432.CCR-17-0408.

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13. Bougeard, G. *et al.* Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. *J. Clin. Oncol.* (2015) doi:10.1200/JCO.2014.59.5728.

14. Palmero, E. I. *et al.* Detection of R337H, a germline TP53 mutation predisposing to multiple cancers, in asymptomatic women participating in a breast cancer screening program in Southern Brazil. *Cancer Lett.* (2008) doi:10.1016/j.canlet.2007.10.044.

15. Zick, A. *et al.* Recurrent TP53 missense mutation in cancer patients of Arab descent. *Fam. Cancer* (2017) doi:10.1007/s10689-016-9951-z.

16. Lolas Hamameh, S. *et al.* Genomic analysis of inherited breast cancer among Palestinian women: Genetic heterogeneity and a founder mutation in TP53. *Int. J. Cancer* (2017) doi:10.1002/ijc.30771.

17. Slee, E. A., O’Connor, D. J. & Lu, X. To die or not to die: How does p53 decide? *Oncogene* (2004) doi:10.1038/sj.onc.1207516.

18. Heymann, S. *et al.* Radio-induced malignancies after breast cancer postoperative radiotherapy in patients with Li-Fraumeni syndrome. *Radiat. Oncol.* (2010) doi:10.1186/1748-717X-5-104.

19. Boyle, J. M. *et al.* The relationship between radiation-induced G1 arrest and chromosome aberrations in Li-Fraumeni fibroblasts with or without germline TP53 mutations. *Br. J. Cancer* (2001) doi:10.1054/bjoc.2001.1896.

20. Hwang, S. J. *et al.* Lung cancer risk in germline p53 mutation carriers: Association between an inherited cancer predisposition, cigarette smoking, and cancer risk. *Hum. Genet.* (2003) doi:10.1007/s00439-003-0968-7.

21. Alexandrov, L. B. *et al.* The repertoire of mutational signatures in human cancer. *Nature* (2020) doi:10.1038/s41586-020-1943-3.

22. Kadouri, L. *et al.* A novel BRCA-1 mutation in Arab kindred from east Jerusalem with breast and ovarian cancer. *BMC Cancer* (2007) doi:10.1186/1471-2407-7-14.

**CURRICULUM VITAE**

**Candidate's name: Aviad Zick**

**1. PERSONAL DETAILS**

**Date of Birth: Jan. 21th, 1974**

**Country of Birth: Israel**

**Date of Immigration: 1974**

**ID no.: 02711374-5**

**Nationality: Israeli**

**Marital status: Married**

**No. of children: 3**

**Military Service:** IDF, first lieutenant (reserve duty). 2011 – Exceptional service in medicine, Northern command**.**

**Permanent address: Mexico 2a, Apt.5, Jerusalem, Israel**

**Home Tel.:** 972-2-6426479

**Work Tel:**

**Cell:** 972-50-4048024

**E-mail address:**  aviadz@hadassah.org.il

**2. HIGHER EDUCATION**

(in chronological order)

|  |  |  |
| --- | --- | --- |
| **M. D.** | 1996 – 2005 | Hebrew University - Hadassah Medical School, Jerusalem |
| **Ph.D.** | 2004-2009 | Hebrew University - Hadassah Medical School, Jerusalem Advisor: Prof. Joseph Shlomai. Articles 1-3 |
| **Medical Epidemiology** | 2010- 2011 | The Hebrew university-Hadassah Braun school of public health and community medicine. |

**3. Employment History**

|  |  |  |
| --- | --- | --- |
| 2012- Present | Senior medical oncologist | Sharett Institute of Oncology, Hadassah Hebrew University Hospital , Jerusalem, Israel |
| 2007-2012 | Medical oncology residency | Sharett Institute of Oncology, Hadassah Hebrew University Hospital , Jerusalem, Israel |
| 2006-2007 | Medical intern | Hadassah Hebrew University Hospital , Jerusalem, Israel |

**4. APPOINTMENTS AT THE HEBREW UNIVERSITY**

|  |  |
| --- | --- |
| 2011-2017 | Clinical Instructor, Hebrew University Hadassah Medical School |
| 2017- | Clinical Lecture, Hebrew University Hadassah Medical School |

**5. ADDITIONAL FUNCTIONS/TASKS AT THE HEBREW UNIVERSITY-HADASSAH MEDICAL CENTER**

(in chronological order)

|  |  |
| --- | --- |
| 2012-2013 | Researcher, Dep. of Oncology, Hebrew University - Hadassah medical center, Jerusalem, Israel. Reseach Project: *Validation of the ampliseq cancer panel on the Ion PGM platform* (Under the guidance of Prof. Eli Pikarsky) |
| 2013-Present | Head of Cancer Genetics laboratory, Department of Oncology, Hebrew University - Hadassah medical center, Jerusalem, Israel. |
| 2014-2016 | Head of oncology teaching for Clinical Years , Hebrew University-Hadassah Medical School, Jerusalem, Israel. |
| 2015-Present  2017-Present | Member of Institutional Helsinki committee, Hebrew University - Hadassah medical center, Jerusalem, Israel.  Member of Interdepartmental equipment committee, Hebrew University - Hadassah Medical School, Jerusalem, Israel. |
| 2018-Present | Head of Sarcoma Forum |

**6. OTHER ACTIVITY**

(in chronological order)

|  |  |  |  |
| --- | --- | --- | --- |
|  | | | |
| 2008 | | Advanced cardiovascular life support (**ACLS**) provider course. Most recent course- Hadassah Medical Center. Israel. | |
| 18/10/2010 | | Participant in a debate of the Knesset joint committee of health and environment on "The connection between pollution in the Haifa bay and lung cancer" | |
| 2014 - Present | | Member of scientific-ethical committee of the Israeli biobank. | |
| 2018 | | Member of the ISCORT scientific committee | |
| 2019 - Present | | Examiner in the final exam of oncological residency of the Israeli medical association. | |
| **7. AWARDS** | | | |
| 2010 | | Young researcher award of the Hadassah medical center | |
| 2011 | | Health Education fund in honor of Lou Sand | |
| 2013 | | David S. Lando Memorial Fund | |

**8. MEMBERSHIP IN A PROFESSIONAL ASSOCIATION**

|  |  |
| --- | --- |
| 2007-Present | Israeli Society for Clinical Oncology and Radiation Therapy |
| 2010-Present | Israeli Society for Cancer Research |
| 2010-2013 | International Society of Oncology and BioMarkers |
| 2013 | American Society of Clinical Oncology |

**9. RESEARCH GRANTS**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 2012 | Monsa Memorial Fund | Genomic features in colon cancer among BRCA1 and 2 carriers. | 22,000 NIS | 1 Year |
| 2013 | Israel Science Foundation | NF-kappaB regulation of DNA double-strand break repair | 200,000 NIS per year | 3 Years |
| 2013 | The Joint Research Fund between the Hebrew University Faculty of Medicine, and between Hadassah University Hospital, Shaare Tzedek Medical Center, Kaplan Medical Center and Bikur Holim Hospital | Homologous recombination repair deficiency in colon carcinoma | $10,000 | 1 Year |
| 2014 | Monsa Memorial Fund | Identification of SV using WGS | 50,000 NIS | 1 Year |
| 2015 | Dr. Ivan Kempner Memorial Fund | HER2 amplicon structure | 17,257 NIS | 1 Year |
| 2016 | Israeli Cancer Association | Characterization of the elevated cancer incidence in the Haifa sub-district, accounting for residence history and personal health variables such as smoking | 75,000 NIS | 1 Year |
| 2016 | Asaf Fund | Spatial analysis of cancer incidence during 16 years in north Israel and correlation to soil metal concentration | 50,000 NIS | 1 Year |
| 2016 | ICRF | Tissue-specific methylation patterns of circulating DNAs as biomarkers for neurotoxicity | 50,000 $ per year | 2 Years |
| 2017 & 2019 | Merck –Investigator initiated trial | CETUXIMAB MONOTHERAPY OR CETUXIMAB + CHEMOTHERAPY FOR THIRD LINE RECHALLENGE IN METASTATIC COLORECTAL CANCER, RAS WILD TYPE PATIENTS, WHO WERE TREATED WITH CETUXIMAB + CHEMOTHERAPY AS FIRST LINE TREATMENT | 390,654 EU | 8 Years |
| 2018 | Cancer Research Fund of Sarita and Elmer Gross z"l | Identification of tissue specific sarcoma markers using single cell analysis | 200,000 NIS | 2 Years |
|  |  |  |  |  |
| 2018 | Cancer Research Fund of Sarita and Elmer Gross z"l | Thyroid Cancer Survivors Risk for a Second Primary Tumor and the Outcome of a Second Primary Cancer | 30,000 NIS | 1 Years |
| 2020 | JFC-UIA | A cell free DNA (cfDNA) based blood test to detect breast cancer | 37,000 NIS | 2 Years |
|  |  |  |  |  |
| 2020 | Karyopharm Therapeutics Inc. – Investigator initiated trial | Identification of predicative biomarkers and the biological activity of Selinexor combination  therapy using cell free methylated DNA and nucleosome analysis. | 138,937$ | 3 Years |
|  |  |  |  |  |
| 2020 | Monsa Memorial Fund | Identification of novel homologous recombination repair genes in ovarian cancer patients | 45,000 NIS | 1 Year |

**10. TEACHING AT THE HEBREW UNIVERSITY**

**A. Courses taught in the last 5 years**

* **Bachelor's degree courses:**

2020 Seminar in computational biology

* **Master's degree courses**

|  |  |
| --- | --- |
| 2015- Present | Personalized medicine |
| 2017- Present | [Molecular Medicine and Oncogenomics](javascript:void()) |

* **Medical School (MD) courses:**

|  |  |
| --- | --- |
| 2010 Present | Problem Based Learning for 2nd and 3rd year medical students. |
| 2012-2013 | Humanities course for medical courses ("Adam verefu'a") - 1st year medical students. |
| 2010-Present | Oncology for 4th year medical students in pre-clinical course. |

2011-Present Lectures given in oncology course for 5th year students, including

Introduction to oncology, chemotherapy treatment, emergency

situations in oncology, clinical implication of DNA characterization

in oncological care, case discussions, bed-side teaching and

evaluation and commenting on student presentations.

2012- Present Lectures given in Epidemiology course for 5th year students

**11. STUDENTS AT THE HEBREW UNIVERSITY**

# **Dolev Rahat - Mapping the Human Homologous Recombination Repair pathway using Clade Phylogenetic Profiling and Omics Data Integration – M.Sc. submitted in 2018**

**LIST OF PUBLICATIONS**

**Aviad Zick**

List of abbreviations for co-author functions: principal investigator PI, student S, co-researcher C, technician / laboratory assistant T.

**DOCTORAL DISSERTATION**

(cross-referenced)

Replicative Helicases and the Progression of the Minicircle's Replication Fork in Trypanosomatids. Supervisor: Prof. Joseph Shlomai, 2008 (diploma awarded June 2009). Publications relating to this work- articles 1-3.

**BOOKS**

(in chronological order; cross-referenced)

**BOOKS EDITED:**

(in chronological order; cross-referenced)

**CHAPTERS IN COLLECTIONS:**

(in chronological order; cross-referenced)

**ARTICLES:**

(in chronological order; cross-referenced)

1. **Aviad Zick**S, Itay OnnS, Rachel BezalelS, Hanah MargalitC, and Joseph ShlomaiPI. Assigning functions to genes: identification of S-phase expressed genes in Leishmania major based on post-transcriptional control elements 2005, *Nucleic Acids Res*.; 33(13): 4235–42

2) Beiyu LiuS, Jianyang WangS, Nurit YaffeS, Megan LindsayS, Zhixing ZhaoS, **Aviad Zick**S**,** Joseph ShlomaiPI, and Paul T. EnglundPI. Trypanosomes Have Six Mitochondrial DNA Helicases with One Controlling Kinetoplast Maxicircle Replication. 2009, *Mol Cell*. 28;35(4):490-501

3) Dotan SelaS, Neta MilmanS, Irit KapellerT, **Aviad Zick**S, Rachel BezalelS, Nurit YaffeS, Joseph ShlomaiPI. Unique characteristics of the kinetoplast DNA replication machinery provide potential drug targets in trypanosomatids. 2008, *Adv Exp Med Biol*.;625:9-21.

4) **Aviad Zick**PI, Limor AppelbaumPI. HER2 as a marker for guiding the choice of chemotherapy in breast cancer patients. 2010, *Harefuah*. 149(12):807-8, 810

5) Rottenberg YPI**,** **Zick A**PI\*, Barchnna MC, Peretz TPI. Organ specific cancer incidence in an industrial subdistrict: a population-based study with 12 years follow-up. 2013, *Am J Can Epidemiol Prev*. 1(1):13/22. N/A citations 1

\*Equal contribution

6) Nava Siegelmann-DanieliS, Barbara SilvermanT, **Aviad Zick**S, Anat Beit-OrT, Itzhak KatzirS, Avi PorathPI. [The impact of the Oncotype DX Recurrence Score on treatment decisions and clinical outcomes in patients with early breast cancer: the Maccabi Healthcare Services experience with a unified testing policy.](http://www.ncbi.nlm.nih.gov/pubmed/24386009) 2013, *Ecancermedicalscience.* Dec 17;7:380.

7) **Aviad Zick**PI, Sherri CohenT, Tamar HamburgerT, Yael GoldbergC, Naama ZviC, Michal SagiC and Tamar PeretzPI.A *BRCA1* Frame Shift Mutation in Women of Kurdish Jewish Descent2015,*Open medicine Journal*, 7, 31-36.

8) Roni WermanS, Daniel NeimanS, Hai ZemmourS, Joshua MossS, Judith MagenheimS, Adi Vaknin-DembinskyC, Sten RubertssonC, Bengt NellgårdC, Kaj BlennowC, Henrik ZetterbergC, Kirsty SpaldingC, Desmond SchatzC, Carla GreenbaumC, Craig DorrelC, Markus GrompeC, **Aviad Zick**C, Ayala HubertC, Myriam MaozT, Volker FendrichC, Talya GolanC, Shmuel Ben-SassonC, Gideon ZamirC, Aharon RazinC, Howard CedarC, AM James ShapiroC, Benjamin GlaserPI, Ruth ShemerPI, Yuval DorPI. Identification of tissue specific cell death using methylation patterns of circulating DNA.2016, *PNAS* Mar 29;113(13):E1826-34.

9) **Aviad ZickPI**, Luna KadouriC, Shani BreuierC, Sherri CohenT, Michael Frohlinger, TamarS HamburgerT, Naama ZviC, Morasha PlaserC, Eilat AvitalC, Yael GoldbergC, Firase ElianC, Azam SalachC, Tamar Peretz**PI**. Recurrent *TP53* Missense Mutation in Cancer Patients of Arab Descent, 2016, *Fam Can*, Nov 19.

10) **Aviad ZickPI\***, Tamar PeretzC\*, Michal LotemC, Ayala HubertC, Daniela KatzC, Mark TemperC, Yakir RottenbergC, Beatrice UzielyC, Hovav NechushtanC, Amichai MeirovitzC, Amir SonnenblickC, Eli SapirC, David EdelmanC, Yael GoldbergC, Alexander LossosC, Shai RosenbergC, Iris FriedC, Ruth FinklsteinT, Eli PikarskyC, Hanoch Goldshmidt**PI**. Treatment Inferred From Mutations Identified Using Massive Parallel Sequencing Leads To Clinical Benefit in Some Heavily Pretreated Cancer Patients. *Medicine* , 2017.

\*Equal contribution

11) [Paz Polak](https://www.nature.com/articles/ng.3934#auth-1)S, [Jaegil Kim](https://www.nature.com/articles/ng.3934" \l "auth-2)S, [Lior Z Braunstein](https://www.nature.com/articles/ng.3934#auth-3)S, [Rosa Karlic](https://www.nature.com/articles/ng.3934#auth-4)C, [Nicholas J Haradhavala](https://www.nature.com/articles/ng.3934#auth-5)C, [Grace Tiao](https://www.nature.com/articles/ng.3934#auth-6)C, [Daniel Rosebrock](https://www.nature.com/articles/ng.3934#auth-7)C, [Dimitri Livitz](https://www.nature.com/articles/ng.3934#auth-8)C, [Kirsten Kübler](https://www.nature.com/articles/ng.3934#auth-9)C, [Kent W Mouw](https://www.nature.com/articles/ng.3934#auth-10)C, [Atanas Kamburov](https://www.nature.com/articles/ng.3934#auth-11)C, [Yosef E Maruvka](https://www.nature.com/articles/ng.3934#auth-12)C, [Ignaty Leshchiner](https://www.nature.com/articles/ng.3934" \l "auth-13)C, [Eric S Lander](https://www.nature.com/articles/ng.3934#auth-14)C, [Todd R Golub](https://www.nature.com/articles/ng.3934#auth-15)C, [**Aviad Zick**](https://www.nature.com/articles/ng.3934#auth-16)**C** [Alexandre Orthwein](https://www.nature.com/articles/ng.3934#auth-17)C, [Michael S Lawrence](https://www.nature.com/articles/ng.3934#auth-18)C, [Rajbir N Batra](https://www.nature.com/articles/ng.3934#auth-19)C, [Carlos Caldas](https://www.nature.com/articles/ng.3934#auth-20)C, [Daniel A Haber](https://www.nature.com/articles/ng.3934#auth-21)C, [Peter W Laird](https://www.nature.com/articles/ng.3934#auth-22)C, [Hui Shen](https://www.nature.com/articles/ng.3934#auth-23)C, [Leif W Ellisen](https://www.nature.com/articles/ng.3934#auth-24)C, [Alan D D'Andrea](https://www.nature.com/articles/ng.3934#auth-25)C, [Stephen J Chanock](https://www.nature.com/articles/ng.3934#auth-26)C, [William D Foulkes](https://www.nature.com/articles/ng.3934#auth-27)PI & [Gad Getz](https://www.nature.com/articles/ng.3934#auth-28)PI. [A mutational signature reveals alterations underlying deficient homologous recombination repair in breast cancer.](https://www.ncbi.nlm.nih.gov/pubmed/28825726) *Nat Genet. 2017* Oct;49(10):1476-1486.

12) Albert GrinshpunS, Nancy GavertC, Roy Ziv GranitC, hadas MasuriC, Ittai Ben-PorathC, Shani BreuerC,**Aviad Zick**C, Shai RosenbergC, Myriam MaozC, Avital GranitC, Eli PikarskyC, Ravid StrausmmanC, Tamar PeretzC, Amir SonnenblickPI.

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Case Reports

1. A case of metastatic adamantinoma responding to treatment with pazopanib*.* Yasmin CohenS, Jonathen e. CohenC, **Aviad Zick**C,Marina OreviC, Victoria DovinerC, Rina RubinsteinC, Hanoch GoldshmidtC, Nili Peylan-RamuC, Daniela KatzPI. 2013, *Acta Oncol. Letters* *,52*, 1229-1230,3.710, 0, 63 of 203 in oncology.
2. 11-year Experience With Chest Wall Resection and Reconstruction for Primary Chest Wall Sarcomas. [Ori Wald](https://pubmed.ncbi.nlm.nih.gov/?sort=date&term=Wald+O&cauthor_id=31992336)S, [Idais Islam](https://pubmed.ncbi.nlm.nih.gov/?sort=date&term=Islam+I&cauthor_id=31992336)C, [Korach Amit](https://pubmed.ncbi.nlm.nih.gov/?sort=date&term=Amit+K&cauthor_id=31992336)C, [Rudis Ehud](https://pubmed.ncbi.nlm.nih.gov/?sort=date&term=Ehud+R&cauthor_id=31992336)C, [Erez Eldad](https://pubmed.ncbi.nlm.nih.gov/?sort=date&term=Eldad+E&cauthor_id=31992336)C, [Or Omer](https://pubmed.ncbi.nlm.nih.gov/?sort=date&term=Omer+O&cauthor_id=31992336)C, [**Zik Aviad**](https://pubmed.ncbi.nlm.nih.gov/?sort=date&term=Aviad+Z&cauthor_id=31992336)**C**, [Shapira Oz Moshe](https://pubmed.ncbi.nlm.nih.gov/?sort=date&term=Moshe+SO&cauthor_id=31992336)C, [Izhar Uzi](https://pubmed.ncbi.nlm.nih.gov/?sort=date&term=Uzi+I&cauthor_id=31992336)PI. J Cardiothorac Surg 2020 Jan 28;15(1):29.

Reviews, commentaries, hypotheses, editorials

**OTHER PUBLICATIONS: (instruction manuals, teaching aids etc.)**

|  |
| --- |
| **Clinical Trial participation as principal investigator**   1. Proteomic analysis of malignant and pre-malignant tissues of colonic origin. 2. I5B-MC-JGDJA, Randomized, Double-Blind, Placebo Controlled, Phase 3 Trial of Doxorubicin plus Olaratumab versus Doxorubicin in Patients with Advanced or Metastatic Soft Tissue Sarcoma 3. ALDOXORUBICIN-P3-STS-01, Randomized, Multicenter, Open, Phase 3 Safety and Efficiency Trial of Aldoxorubicin versus Investigator Choice in Patients with Recurent or Refractory to Adjuvant Treatment Advanced or Metastatic Soft Tissue Sarcoma . 4. CETUXIMAB MONOTHERAPY OR CETUXIMAB + CHEMOTHERAPY FOR THIRD LINE RECHALLENGE IN METASTATIC COLORECTAL CANCER, RAS WILD TYPE PATIENTS, WHO WERE TREATED WITH CETUXIMAB + CHEMOTHERAPY AS FIRST LINE TREATMENT 5. A Phase 2-3 Multicenter, Randomized, Double-blind Study of Selinexor (KPT-330) versus Placebo in Patients with Advanced Unresectable Dedifferentiated Liposarcoma (DDLS). 6. An Open-Label, Phase 2 Study of Neratinib in Patients With Solid Tumors With Somatic Human Epidermal Growth Factor Receptor (EGFR, HER2, Her3) Mutations or EGFR gene amplification. 7. Open-Label Phase 1 Study Evaluating the Pharmacokinetics and Bioequivalence of Different Formulations of Selinexor and the Tolerability and Anti-Tumor Activity of Selinexor Combination Treatment (SPRINT). 8. The relation between p53 mutation status and the mutational burden in Colorectal Cancers.   **Clinical Trial participation as co-investigator**   1. Testing a representative cohort of breast and ovarian cancer for BRCA1/2 and pathological features in an anonymous fashion. PI – Luna Kadouri. 2. Phase II randomized, double blind, and multicenter study to assess the efficacy of AZD2281 in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with two or more platinum containing regimens. PI – Edelmann 3. Testing the cause of health outcomes to environmental causes. PI – Yakir Rotenberg |
| 1. A randomized phase 3, multicenter, open label study comparing TH-302 in combination with Doxorubicin vs. Doxorubicin alone in subjects with locally advance unresectable or metastatic soft tissue sarcoma. PI – Daniela Katz 2. Characterization of genetic material, including total genome/exome sequencing, from tumor cells as a predictive and prognostic measure, and as a tool to follow up treatment in cancer patients. PI – Tamar Peretz 3. A prospective study of results of Recurrence Score Oncotype Dx Breast, and recurrent disease in early breast cancer patients treated in the "Clallit" HMO. PI – Tamar Peretz 4. A single arm multi-center study investigating the at home administration of trastuzumab subcutaneous vial for the treatment of patients with HER2-positive early breast cancer. PI – Beatrice Uziely 5. A phase 3 randomized, placebo-controlled trial of carboplatin and paclitaxel with or without the PARP inhibitor veliparib (ABT-888) in HER2 negative metastatic or locally advanced unresectable BRCA-associated breast cancer. PI – Beatrice Uziely 6. A randomized, dobule-blind, placebo-controlled, phase 3 study of nonsteroidal aromatase inhibitors (anastrozole or letrozole) plus LY2835219, a CDK4/6 inhibtor, or placebo postmenopausal women with hormonereceptor –positive, HER2 negative Locoregionally recurrent or metastatic breast cancer with no prior systemic therapy in this disease setting. PI – Beatrice Uziely 7. Assessing response to canabiadol treatment in progressing cancer patients not receiving active treatment 8. A phase III, open label, randomized, controlled, multi-centre study to assess the efficacy and safety of olaparib monotherapy versus physician’s choice single agent chemotherapy in the treatment of platinum sensitive relapsed ovarian cancer in patients carrying germline BRCA1/2 mutations. PI – Edelmann 9. A phase 3 clinical trial of pembrolizumab (MK-3475) in first line treatment of recurrent/metastatic head and neck squamous cell carcinoma. PI – Yakir Rotenberg. 10. A phase III randomized, open label multi-center, global study of MEDI4736 monotherapy and MEDI4736 in combination with tremelimumab versus standard of care therapy in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN). PI – Amichay Meirovitz 11. A phase II, multi-center, single-arm, global study of MEDI4736 monotherapy in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN). PI – Amicay Meirovitz 12. A Phase II, randomized, open-label, multi-center, global study of MEDI4736 monotherapy, tremelimumab monotherapy, and MEDI4736 in combination with tremelimumab in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN). PI – Amichay Meirovit 13. Epithelial ovarian carcinoma – database PI – David Edelman. |

(in chronological order)

**Patents**

**CONFERENCES:**

(in chronological order)

**Invited lectures first**

1. Role of BRCA Status in Treatment Planning, Israeli-French breast cancer update. **Zick A**, Jerusalem,2014, Invited lecture.
2. Increased cancer incidence in the Haifa subdistrict, **Zick A**, Air pollution in the Haifa Bay, Haifa, 2016, Invited lecture.
3. Shallow whole genome sequencing for CNV detection, **Zick A**, Bioinfo-Forum Meeting, Ariel, 2016, Invited lecture.
4. Analysis of the Geographical Distribution of Cancer in Israel. **Zick A**, Yakir Rottenberg, Micha Barchana, Tamar Peretz. ISCORT, Eilat, 2009, lecture.
5. Analysis of the Geographical Distribution of Cancer in Israel. **Zick A**, Yakir Rottenberg, Micha Barchana, Tamar Peretz. ASCO, USA, Chicago, 2010, poster.
6. Increased Cancer Incidence in an Industrial Sub-district of Israel. **Zick A**, Yakir Rottenberg, Micha Barchana, Tamar Peretz. ISCR, Rehovot, 2010, poster.
7. Can Cadmium Serve as a Screening Marker for cancer? **Zick A**, Yakir Rottenberg, Micha Barchana, Tamar Peretz. ISOBM, Munich, Germany, 2010, poster.
8. Environmental Exposure to Cadmium is Associated with Increased Risk of Cancer. **Zick A**, Yakir Rottenberg, Micha Barchana, Tamar Peretz. ILANIT, Eilat,2011, poster.
9. A Case of Metastatic Adamantinoma Responding to Treatment with Pazopanib. Cohen Y, Cohen J.E., **Zick A**, Orevi M, Doviner V, Rubinstein R, Goldschmidt H, Peylan-Ramu N and Katz D. (ISCORT12), Eilat, January 2013. Presentation by Dr Cohen J.E
10. Using the Recurrence Score in Clinical Practice: An HMO Experience With a Unified Testing Policy. [Siegelmann-Danieli](http://www.ncbi.nlm.nih.gov/pubmed/?term=Siegelmann-Danieli%20N%5Bauth%5D) N, [Silverman](http://www.ncbi.nlm.nih.gov/pubmed/?term=Silverman%20B%5Bauth%5D) B, [**Zick**](http://www.ncbi.nlm.nih.gov/pubmed/?term=Zick%20A%5Bauth%5D) **A**, [Beit-Or](http://www.ncbi.nlm.nih.gov/pubmed/?term=Beit-Or%20A%5Bauth%5D) A, [Katzir](http://www.ncbi.nlm.nih.gov/pubmed/?term=Katzir%20I%5Bauth%5D) I, and [Porath](http://www.ncbi.nlm.nih.gov/pubmed/?term=Porath%20A%5Bauth%5D) A, 13th St. Gallen International Breast Cancer Conference, Switzerland, St. Gallen, 2013 Poster.
11. Validation of the Ampliseq™ Cancer Panel Using the Ion PGM™ Reveals Mutations with Possible Clinical Implications in *KIT, JAK3* and *PTEN* Genes. **Zick A**, Goldshmidt H, Finklstein R, Kopolovic J, Pikarsky E, PeretzT

ISGCT, Jerusalem 2013, Poster.

1. Improved Survival After Cancer Diagnosis Among Patients With Higher Income and Education: A Population Based Study. 5th International Jerusalem Conference on Health Policy. Rottenberg Y, **Zick A**, Peretz T, Jerusalem 2013, Poster.
2. Reversal of acquired resistance to pazopanib in soft tissue sarcoma with addition of an mTOR inhibitor: A case report. Katz D, **Zick** A, Cohen J. E., Sonnenblick A, Fridman E, Shaham D, Peretz T. ASCO, USA, Chicago, 2013, Poster.
3. Survival After Cancer Diagnosis Among Patients with Higher Income and Education in Israel, a Country with Highly Appreciated Health Service. Rottenberg Y, **Zick A**, Peretz T, ASCO, USA, Chicago, 2013, Poster.
4. A Clinical Service Using the AmpliseqTM Cancer Panel Reveals Mutations with Possible Clinical Implications in the *ATM*, *GNAS*, *KRAS*, *ABL1* and *ERBB2* Genes. **Zick A**, Goldshmidt H, Finklstein R, Kopolovic J, Pikarsky E, PeretzT, ISCR, Beer-Sheva, 2013, Lecture.
5. The Association Between Income and Education on Survival in Israel, Country with Highly Appreciated Health Service,Rottenberg Y, **Zick A**, Peretz T, ISCR, Beer-Sheva, 2013, poster.
6. Clinical Implications of Massive Parallel Sequencing, a Single

Institution Experience, **Zick A**, Goldshmidt H, Finklstein R, Kopolovic J, Pikarsky E, PeretzT, ISCORT, Eilat, 2013, lecture.

1. Treatment Inferred from Mutations Identified Using Massive Parallel

Sequencing Leads to Clinical Benefit in some Heavily Pretreated Cancer Patients. **Zick A**, Goldshmidt H, Finklstein R, Kopolovic J, Pikarsky E, PeretzT, ILANIT Eilat, 2014, poster.

18. Novel Techniques and Platform for Massive Parallel Sequencing of DNA Extracted from Formalin Fixed and Paraffin Embedded (FFPE) Tumor Tissues: Maoz M, **Zick A**, Rosenberg S, Herbst M, Lavon I, Kott-Gutkowski M, Goldshmidt H, Meir K, Pikarsky E, PeretzT,ILANIT Eilat, 2014, poster

19. Massive Parallel Sequencing of 22 Gene Panel for Breast Cancer Susceptibility Genes, CohenS, **Zick A**, Hamburger T, Lerer I, PeretzT ILANIT Eilat, 2014, poster

20. *BRCA1* Frame Shift Mutation in Women of Kurdish Jewish Descent, **Zick A**, CohenS,, Hamburger T, Goldberg Y, Zvi N, Sagi M, PeretzT ISCR, Rechovot, 2015 poster

21. DNA Amplifications Identified Using Whole Genome Massive Parallel Sequencing Inferred Novel Treatments in Metastatic Patients, **Zick A**, Maoz M, Devir M, Israeli M, Rosenberg S, Fishbain Yoskovitz V, Hubert A, Uziely B, Nechushtan H, Goldshmidt H, Meir K, Pikarsky E,Peretz T. Clinical Genomic Analysis Workshop, Haifa, 2015, Poster

22. Treatment Inferred From Mutations Identified Using Massive Parallel Sequencing Leads To Clinical Benefit in Some Heavily Pretreated Cancer Patients, **Zick A**, Peretz T, Lotem M, Hubert A, Katz D, Temper M, Rottenberg Y, Uziely B, Nechushtan H, Meirovitz A, Sonnenblick A, Sapir E, Edelman D, Goldberg Y, Lossos A, Rosenberg S, Fried I, Finklstein R, Pikarsky E, Goldshmidt H, ESMO, Copenhagen, Denmark 2016, Poster

23. Detection of Breast Cell Death Using Methylation Patterns of Circulating DNA. Ofri Abraham, Joshua Moss, Miriam Maoz, Aharon Razin, Itai Ben-Porath, Benjamin Glaser, Tamar Sella, Beatrice Uziely, **Aviad Zick**, Ruth Shemer, Yuval Dor, ILANIT Eilat, 2017, poster

24. A *TP53* Missense Mutation in Breast Cancer Patients of Arab Descent

**Aviad Zick**, Sherri Cohen, Michael Frohlinger, Tamar Hamburger, Naama Zvi, Morasha Plaser, Yael Goldberg, Shani Breuier, Firase Elian, Azam Salach, Luna Kadouri, Tamar Peretz, ILANIT Eilat, 2017, lecture

25. Amplicon Structure in Early and Advanced HER2 Positive Tumors. Myriam Maoz, Michal Devir, Michal Inbar, Dana Sherill-Rofe, Idit Bloch, Moshe Israeli, Karen Meir, Lubov Divinski, David Edelman, Salah Azzam, Hovav Nechushtan, Ofra Maimon, Beatrice Uziely, Luna Kaduri, Amir Sonnenblick, Amir Eden, Tamar Peretz, **Aviad Zick** EACR-AACR-ISCR Jerusalem, 2018, poster

26. Utilizing big data in medical oncology. **Aviad Zick** Updates in Oncology on the treatment spectrum of the Hospital to community and community to hospital Jerusalem, 2019, lecture

27. Patient-Specific drug therapies for P63- related ectodermal dysplasia, New therapeutic approaches and agents suitable for Personalized Medicine, Jerusalem, 2016, chair

28. Markers and Genomics, The Jerusalem Conference for Oncological Patient Care, Jerusalem, 2016, chair

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Description** | **Per Month / Per sample** | **Months / No of samples** | **Total (NIS)** |
| **Personal** | Bioinformatician(Yontan Monin) |  | 12 | 0 |
|  | M. Sc (TBN) | 3814 | 12 | 45768 |
| **Services** | Tissue collection from pathology | 400 | 15 | 6000 |
|  | WGS | 2680 | 15 | 40200 |
| **Overhead** |  |  |  | 8000 |
| **Total** |  |  |  | 99968 |

**Budget**

**Active grants –** There is no over lap between the grants.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 2017 & 2019 | Merck –Investigator initiated trial | CETUXIMAB MONOTHERAPY OR CETUXIMAB + CHEMOTHERAPY FOR THIRD LINE RECHALLENGE IN METASTATIC COLORECTAL CANCER, RAS WILD TYPE PATIENTS, WHO WERE TREATED WITH CETUXIMAB + CHEMOTHERAPY AS FIRST LINE TREATMENT | 390,654 EU | 8 Years |
| 2018 | Cancer Research Fund of Sarita and Elmer Gross z"l | Identification of tissue specific sarcoma markers using single cell analysis | 200,000 NIS | 2 Years |
|  |  |  |  |  |
| 2018 | Cancer Research Fund of Sarita and Elmer Gross z"l | Thyroid Cancer Survivors Risk for a Second Primary Tumor and the Outcome of a Second Primary Cancer | 30,000 NIS | 1 Years |
| 2020 | JFC-UIA | A cell free DNA (cfDNA) based blood test to detect breast cancer | 37,000 NIS | 2 Years |
|  |  |  |  |  |
| 2020 | Karyopharm Therapeutics Inc. – Investigator initiated trial | Identification of predicative biomarkers and the biological activity of Selinexor combination  therapy using cell free methylated DNA and nucleosome analysis. | 138,937$ | 3 Years |
|  |  |  |  |  |
| 2020 | Monsa Memorial Fund | Identification of novel homologous recombination repair genes in ovarian cancer patients | 45,000 NIS | 1 Year |

**Time line**

|  |  |  |
| --- | --- | --- |
| **Part** | **Details** | **Time** |
| **1** | Patient recruitment and data collection | 6 months |
| **2** | Retrieving pathological samples and ddPCR | 2 months |
| **3** | WGS | 2 months |
| **4** | Data integration | 2 months |
|  | Total | 12 months |