**Internal report – Period 1**

**WP4 – “Assess metabolic networks for model parameterization and validation”**

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| Summary | In collaboration with WP3, the experimental scientists have obtained the cell lines that will serve as initial model systems for the entire consortium. The use of identical serum lots is critical and this aspect has been taken care of.  A suitable protocol for extraction of NAD metabolites from cell lines has been established. NIN has started setting up Elisa assays for Trp metabolites. |

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| **Approved by the Work Package Leader**  **Mathias Ziegler** | **Date**  **9 No 2018** |

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| **Date** | **Change** | **By whom** | **Comments** |
|  |  |  | First version |
|  |  |  |  |

**Document history**

**Part A**

1. **Publishable summary**

*Please complete 1.1 and 1.2 with suitable quality to enable direct publication by the European Commission. It should be easy to read, i.e. written in a language easily understandable by a broader public, thereby promoting the dissemination and supporting the exploitation of EU funded results. This part must not contain any confidential data.*

* 1. **Work performed in your WP from the beginning of the project to the end of this reporting period and main results achieved so far**

In close collaboration with WP3, important steps have been undertaken to coordinate experiments that need to be conducted simultaneously to properly parameterize comprehensive models including both signaling and metabolic networks. Thus, WP4 members CO and MZ, who will conduct experiments for metabolic measurements, have obtained the cell lines that will serve as initial model systems for the entire consortium (MCF7, BT-474, ZR-751, T47-D, MDA-MB415).

The use of identical serum lots is critical and this aspect has been taken care of. CS (WP3) will complete serum testing in 2018.

A suitable protocol for extraction of NAD metabolites from cell lines has been established. NIN started work in developing the following immune assays for the following targets: N1-Methylnicotinamide, Quinolinic acid, Kynurenic acid, Xanthurenic acid.

* 1. **Progress beyond the state of the art, expected results of your WP until the end of the project and potential impacts (including the socio-economic impact and the wider societal implications of the project so far).**

1. **Critical implementation risks and mitigation actions**
   1. **Foreseen risks**

*Please see list of risks in Annex 1 of the Grant Agreement (pages 32 – 34) and describe whether your risks materialized and whether you applied mitigation measures in the table below.*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Risk No.** | **Risk** | **WP** | **Proposed mitigation measures** | **Did you apply risk mitigation measures** | **Did your risk materialize?** | **Comments** |
|  |  |  |  | Yes/No | Yes/No | Insert comment if needed, mandatory if the risk mitigation measures have not been applied |

* 1. **Unforeseen risks**

*Please list any unforeseen risks and proposed mitigation measures in the table below.*

|  |  |  |  |
| --- | --- | --- | --- |
| **Risk No.** | **Description of risk** | **WP** | **Proposed mitigation measures** |
|  |  |  |  |

1. **Dissemination and exploitation of results**
   1. **Scientific publications**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of publication** | **Title of the scientific publication** | **DOI** | **ISSN or eSSN** | **Title of the journal or equivalent** |
| Article in journal  Publication in conference proceeding/ workshop  Books/ Monographs  Chapters in books  Thesis/ Dissertation | Insert Title | Insert DOI reference | Insert ISSN or eSSN number | Insert title of the journal |

*In case there is no DOI available for your publication, please indicate the following; Number of the journal, month and year of publication, Publisher, Place of publication, Relevant pages, whether it was a public or private publication, whether it was peer-reviewed, whether open access is/will be provided to this publication (green open access, gold open access, no open access).*

* 1. **Dissemination and communication activities**

*Please detail your dissemination and communication activities in tables on pages 7 – 11.*

* 1. **Intellectual property rights resulting from the project**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Type of IP rights** | **Application reference** | **Date of the application** | **Official title of the application** | **Applicants** | **Has the IPR protection been awarded?** | **If available, official publication number of award of protection** |
| Patent  Trademark  Registered design  Utility model  Other | For international applications of patents: insert IP international organization code, insert serial number  For national applications of patents: insert country code (two letters), insert serial number | dd/mm/yyyy |  | Insert beneficiary(ies) name | Yes/No/Not applicable | For patents: insert code (two letters referring to a country or organization, insert serial number)  For rest: insert official publication number |

1. **Open Research Data**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Digital Object Identifier, DOI (if available)** | **Title/Identifier** | **Is this dataset openly accessible?** | **Is this dataset reusable?** | **If the dataset is linke to a publication, specify the DOI of the publication** |
| Insert DOI reference | Insert Title or Identifier | Yes/No | Yes/No | Insert DOI reference of the publication |

1. **Gender**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Beneficiaries** | **Number Women Researchers (all levels, incl. postdocs and PhD students)** | **Number Men Researchers (all levels, incl. postdocs and PhD students)** | **Number Women in the workforce other than researchers** | **Number Women in the workforce other than researchers** |
| Insert name of beneficiary | Insert number | Insert number | Insert number | Insert number |

**Part B**

1. **Explanation of the work carried out by the beneficiaries and overview of the progress**
   1. **Progress towards objectives and details for each task**

*Please include an overview of the project results towards the objectives of the action. Therefore, please list the specific objectives for your WP as described in Annex 1 to the Grant Agreement and describe the work carried out during this reporting period towards the achievement of each listed objective. Please provide clear and measurable details.*

So far, the principal prerequisites for the metabolomics work were addressed. All activities have been coordinated with CS (Leader WP3) to work with the exact same cell lines and procedures. These activities include the selection of suitable cell lines and acquisition of cell culture medium components, in particular, fetal bovine serum.

The extraction procedures for

* 1. **Explanation of the work**

*Please describe the work carried out in your WP during the reporting period. Give details of the work carried out by each beneficiary involved.*

* 1. **Impact**

*Please describe in this section whether the information on section 2.1 of the Description of Action (how your project will contribute to the expected impacts) is still relevant or needs to be updated. Include further details in the latter case.*

1. **Update of the plan for exploitation and dissemination of results (if applicable)**

*Include in this section whether the plan for exploitation and dissemination of results as described in the DoA needs to be updated and give details.*

1. **Update of the data management plan (if applicable)**

*Include in this section whether the data management plan as described in the DoA needs to be updated and give details.*

1. **Deviations from Annex 1 and Annex 2 (if applicable)**

*Explain the reasons for deviations from the DoA, the consequences and the proposed corrective actions.*

* 1. **Tasks**

*Include explanations for tasks not fully implemented, critical objectives not fully achieved and/or not being on schedule. Explain also the impact on other tasks, on the available resources and the planning*

* 1. **Use of resources**

*Please use the table below to give information about the effort of each partner involved in your WP measured as the amount of person months (pm). See WP descriptions in Annex 1 to the Grant Agreement for the amount of planned WP efforts. Please include explanations on deviations of the use of resources between actual and planed use of resources in Annex 1 (if applicable), especially related to person months per WP.*

|  |  |
| --- | --- |
| **MESI-STRAT partner** | **Person months (pm)** |
|  | [Insert number pm] |
|  |  |

*In addition, if applicable, please Include explanations on transfer of costs categories.*

* + 1. **Unforeseen subcontracting (if applicable)**

*Please specify:*

1. *the work (the tasks) performed by a subcontractor which may cover only a limited part of the project;*
2. *explanation of the circumstances, which caused the need for a subcontract, taking into account the specific characteristic of the project;*
3. *the confirmation that the subcontractor has been selected ensuring the best value for money or, if appropriate, the lowest price and avoiding any conflict of interests.* 
   * 1. **Unforeseen use of in kind contribution from third party against payment of free of charges (if applicable)**

*Please specify:*

1. *the identity of the third party*
2. *the resources made available by the third party respectively against payment or free of charges*
3. *explanation of the circumstances which caused the need for using these resources for carrying out the work*

*Table 1: Communication activities*

| **Key goals** | **Target**  **Audience** | **medium and means**  \*one-way or \*\*two-way communication | **timing of**  **implementation** | **Impact monitoring**  = reaction of  target audience | **What has been done?** (Who, what, when, indicate impact, e.g. no. of attendees etc.) | **What will you contribute by June 2019?** (Who, what, when, indicate impact, e.g. no. of attendees etc.) |
| --- | --- | --- | --- | --- | --- | --- |
| **• Accelerate the translation of MESI-STRAT biomedical and clinical research results to medical use, guided by patients’ needs.**  • Promote rapid and better use of systems medicine research results  • Support mutual learning, science literacy  • Target MESI-STRAT to patients’ needs  • Perform participatory research | cancer  patients  specifically ER+ BC  patients | **\*\*MESI-STRAT patient days** (co-)organized by clinical and associated partner BC centers and the **BC patient organization PATH** with advice by **the Cancer Information Service KID** (DKFZ) | from project start on, throughout/ after project,  goal: twice at partnering and associated BC centers | ≥ 200 attendees /a, on average |  |  |
| **\*\* Presence at patient days and patient-internet platforms** to present project results and new directions in BC therapy, e.g. at partner BC centers, Breast Health Day (Europa Donna, on our IAB) <http://www.breasthealthday.org/>, ‘diploma patient’ congress focused on breast cancer patients.  <http://www.diplompatientin.de/index.html> | throughout and after project  3 times/a | ≥300 attendees, visitors /a |  | e.g. C. Opitz invited to mamazone’s “Diplompatientin” 02.11.18 |
| **\*\*Telephone survey** of BC patient needs related to MESI-STRAT, performed by the German Cancer Information Service (DKFZ) | once, at project start | Representative sample out of ≥6,000 contacts/a |  |  |
| **\*\*questionnaires** on needs of patients related to MESI-STRAT, circulated at patient days and on internet by PATH | start in year 2, throughout and after project | ≥100 responses /a from 2nd year on |  |  |
| **\*\*publications in journals and on websites read by BC patients**, e.g., EUPATI European Patient Academy [www.eupati.eu](http://www.eupati.eu), MammaMia (ca. 20,000 copies, <https://mammamia-online.de>), mamazone MAG, Alliance again BC | from beginning throughout the project | at least 2/a |  |  |
| • Align MESI-STRAT with needs & expectations of society in accordance with responsible research and innovation (RRI), with **particular emphasis on gender issues**  • Foster socially relevant research and innovation outcomes of MESI-STRAT | European citizens  (including all stakeholders) | **\*MESI-STRAT**  **website** | throughout the project | monitor traffic on website (count clicks, downloads, divided by country) |  |  |
| **\*Newsletters**   * electronic MESI-STRAT newsletters * PATH print newsletter | during project, 2 newsletters/a  before, during and after project, 1 newsletter/a | monitor download rates by country  7,500 copies |  |  |
| **\*\*polls/surveys** on interest in systems oncology, understanding of principles, expectations regarding research goals and ethical aspects via the MESI-STRAT website | start in year 2, throughout the project | monitor response rate per country ≥200/ a  🡪 present / implement results at annual meetings |  |  |
| \*\***MESI-STRAT gender committee** (GC) will discuss results relevant to male BC at meetings of BC societies | start in year 2, throughout the project | ≥2 presentations/ a |  |  |
| Present project results with focus on chances, risks, and implementation of systems oncology to  foster • awareness  • mutual learning  • science literacy  • easier access to scientific results | healthcare providers, health professionals | skills & training:  **\*\*open workshops** as part of annual MESI-STRAT meetings | each year throughout the project | ≥15 attendees/a |  |  |
| medical and basic science students  at partner institutions and beyond | skills & training:  \*\*implement strategies and research of MESI-STRAT in  **academic teaching** (courses and internships in partner’s laboratories) | throughout and after the project | ≥50 attendees/a |  |  |
| skills &  educational training for   * patients and their families * EU citizens | \*\*invited lectures of MESI-STRAT partners in the context of **public lectures at partner universities, medical centers** and patient initiatives such as diplompatientin.de | from beginning throughout the project | ≥2 public lectures/a |  |  |
| Convey added value of transnational cooperation to lever **systems oncology for patient stratification to inform clinical decision making** | EU citizens | **joint press releases** of partner institutions for annual meetings, patient days, scientific publications from the consortium | from beginning throughout and after the project | ≥3 joint press releases/a |  |  |
| **EU and MESI-STRAT logo** and/or  **project number** on all dissemination/ exploitation/communication actions | ≥20 releases/a that carry the MESI-STRAT/EU signature |  |  |
| **Consideration of regulatory aspects of clinical practice:**  • Promote systems oncology in clinical guidelines  • Enable implementation of systems oncology in disease management  • Consider MESI-STRAT results for future grant programmes and industrial engagement | policymakers:  clinical opinion leaders | **invitation of clinical opinion leaders**  - to annual MESI-STRAT meetings  - to patient days | from beginning throughout and after the project | ≥3 opinion leaders participate in meetings and patient days |  |  |

*Table 2: Dissemination and non-commercial exploitation activities*

| **Key goals** | **Target**  **audience** | **Medium and means**  \*one-way  \*\*two-way interaction | **Timing**  of  implementation | **Impact**  **monitoring**  = expected reaction of  target audience | **What has been done?** (Who, what, when, indicate impact, e.g. no. of attendees etc.) | **What will you contribute by June 2019?**  (Who, what, when, indicate impact, e.g. no. of attendees etc.) |
| --- | --- | --- | --- | --- | --- | --- |
| • **Promote new models for patient stratification to inform clinical decision making.**  • Set new method standards to connect metabolic and signaling models for systems oncology (methodological approaches, data/modeling standards) | systems  biologists  &  systems  medicine  scientists | **\*\*present new models at systems biology conferences**, e.g., ICSB, SBHD, and others | throughout and after project | - conference  invitations  (≤2/a)  - size of audience (≥50) |  |  |
| \***open access publications** **in high-impact systems biology journals,** e.g. Nat. Commun., MSB, Science Signal., PloS Comput. Biology, EMBO J., etc. | start in year 2,  throughout and after project | - number of papers (≥3/a)  - number of citations, impact of citing journals |  |  |
| \*\***final symposium** at the end of MESI-STRAT project including hands-on workshops | end of project | number of attendees (≥200) |  |  |
| • **Accelerate the translation of MESI-STRAT biomedical and clinical research results to medical use,** in particular new MESI marker panels and models for clinical decision making | BC  researchers  (basic and  clinical)  BC healthcare professionals  BC patients | **\*\*present ER+ BC diagnostics/therapy results at cancer conferences**, e.g. at   * Annual European Breast Cancer Conference (EBCC) * Annual meeting of the German Society for Senology (DGS). AS, UHH is vice president 2017 ([senologiekongress.de](http://senologiekongress.de)). * SABCS, ABC (Advanced Breast Cancer) and annual meetings of AGO (AG Gyn. & Oncology), GBG (German Breast Group), St. Gallen Consensus Conference, etc. | throughout and after project | - conference invitations  (≤5/a)  - size of audience (≥100) |  |  |
| \***open access publications in high-impact and highly visible medical journals**, on clinical studies and new routes to BC therapy, e.g., NEJM, Clin Breast Cancer, Eur J Cancer, etc. | start in year 2, continued after project  (partners, collaborators) | - number of papers (3/a)  - number of citations, impact of citing journals |  |  |
| **\*\*identify and use synergies with other consortia and initiatives on BC systems medicine,** e.g., European Working group of BC Research, BASIS (breast cancer somatic genetic study), the ICGC (International Cancer Genome Consortium), the Oslo2 biobank, METABRIC, ITN EpiPredict, etc. | since early project preparation (project representatives invited for MESI-STRAT IAB)  continued throughout and after project | - joint publications with other BC related consortia and initiatives (3 during the project)  - number of citations, impact of citing journals |  |  |
| • Promote the emerging field of systems oncology | cancer  researchers/  oncologists  (basic and  clinical) | **\*\*present new strategies in oncology research at cancer conferences,** e.g. ASCO, ESMO-ECCO, AACR & Cell Symposia, DKK (German Cancer Congress) | throughout and after project | - conference  invitations (≤2/ a)  - size of audience (≥50) |  |  |
| **open data access publishing in cancer journals:**  1) new strategies in systems oncology, e.g., in Nature, Science, Nat. Comm.  2) new molecular mechanisms in cancer, e.g. in Cell, Cancer Cell, Cancer Discovery | start in year 2,  continued after project  (partners, collaborators) | - number of papers (3/year)  - number of citations, impact of citing journals |  |  |
| • **Promote the implementation of novel MESI-STRAT concepts (models and marker panels) by the health care sector to** **increase cost effectiveness in comparison to already established practices** | health care managers and policy makers  (insurances, hospitals, politicians) | **\*\* invite health care managers from the partnering hospitals** to the annual MESI-STRAT meetings. Increase network inviting further hospital representatives in subsequent years  **\*\* invite health insurance representatives and politicians** active in health politics to annual meetings and final conferences | annually, start in year 2  year 4+5 | - number of participants from health care policy at conferences (≤2/ a; 5 at concluding conference) |  |  |

*Table 3: Exploitation activities*

| **Goals** | **Target**  **audience** | **Medium and means**  \*one-way  \*\*two-way interaction | **Timing**  of implementation | **Impact monitoring**  = reaction of  target audience | **What has been done?** (Who, what, when, indicate impact, e.g. no. of attendees etc.) | **What will you contribute by June 2019?**  (Who, what, when, indicate impact, e.g. no. of attendees etc.) |
| --- | --- | --- | --- | --- | --- | --- |
| • **Increase research and innovation opportunities, particularly for SMEs active in diagnostics and pharma companies**  🡪 gain internal and external partners for out-licensing and commercialization    🡪 evaluate own commercial involvement | companies in pharma sector  &  diagnostics | \*\*develop diagnostic tests/devices/services with **partner NIN** and **collaborators QuantuMDX and CELLEC BIOTEK**  \*\*work/collaborate with companies that sell relevant drugs and conduct large clinical trials (e.g., Novartis, see letter), and contacts already established via the clinical trials in which MESI-STRAT participates | from the beginning, throughout and after the project | number of interactions with companies (≥10/a) |  |  |
| \*\* approach new collaborating companies  - via existing networks (of TTOs and of partners)  - by presenting patents at patent information fairs and conferences  - via feasibility study by partner TTOs | at time of discovery and patenting of potential new targets/treatments/predictive models | - number of  patent applications  (≤4)  - number of  licensing requests  (≥2/a) |  |  |
| • **Increase research and innovation opportunities, particularly for SMEs active in systems medicine** | **partnering SMEs:**  service providers for systems medicine | **\*\*HITS partners a broad range of systems biomedicine infrastructure projects.** Participation in MESI-STRAT gains sustainability experience and promotes use of open source and open data. | since early project planning, throughout and after the project | functionality customization and first-hand advice  (≥10 interactions/a within MESI-STRAT and with external customers) |  |  |
| \*\***SBS develops and customizes computational models for the pharma sector.** In MESI-STRAT,SBS customizes models for pharma use and hires students educated at academic partners, licenses models, and commercializes them with pharma partners. | since early project planning, throughout and after the project | request for development of customized computational model-based analyses for drug development/Drug Candidate/Target Assessment Projects  (≥10 interactions/a within MESI-STRAT and with external customers) |  |  |