FUNDING APPLICATION FOR

EXPLORATORY RESEARCH PROJECTS - PN-II-P4-ID-PCE-2020-2

Section 2

Automatic Detection of Fast-Acid Bacilli in Microscopic Slides Using Artificial Intelligence (AIZN)

This document uses Times New Roman font, 12 point, 1.5 line spacing and 2 cm margins. Any changes of these parameters (except tables, figures or legends) are prohibited. Excess pages will not be considered by the experts in the evaluation process. The imposed number of pages does not contain the references; these will be written on additional pages.

The black text must be kept as it marks the mandatory information and sections of the application.

B. Project leader

B1. Important scientific achievements of the project leader (maximum 3 pages)

Please, present the most important contributions of the project leader in his/her research field (for instance, discoveries or results which significantly led to better knowledge in the field). In the presentation, please underline the following aspects: (1) the relation of these contributions to the topic of the proposed project; (2) the reflection of these contributions in his/her publications (particularly those published as the main author), particularly those listed in the significant publications list B3.1 section and/or other publications included in the profile of the project leader (the project leader will choose between Scopus Author ID, ORCID, Researcher ID, Google Scholar or MR Author ID); (3) the way in which these scientific contributions illustrate the independent research activity of the project leader and his/her international visibility (by references to the B3.2 section).

Since pathology becomes more and more technical every year, with increased measurement types, additional scales and improved classifications, technicalities that are imposed by our current pursuit of bringing personalized medicine in daily practice, an artificial intelligence (AI) approach of the histopathologic diagnosis looks like the obvious solution to any physician except pathologist itself. The reason behind this assertion resides in the particularities of the histopathologic analysis that is much closer to clinical diagnosis than to a laboratory investigation; one should have sound histopathological background to understand that a pathologist is analysing a myriad of discrete elements to establish a diagnosis and he/she is not measuring a parameter. Thus, any project involving methods of machine learning in pathology should rely on pathologist's expertise, an increased quality of pathologist' diagnostic ability (implicitly the diagnostic value of the pictures provided for AI analysis), would lead to appropriate results; moreover, the managerial expertise of the pathologist conducting such an endeavor has outmost importance since the quality, reproducibility and diagnostic certainty rest in his/her organizing abilities.

We intend to develop a program able to identify acid-fast bacilli in Ziehl Nielsen (ZN) slides. The pathologist conducting such a project should be familiar with histopathologic appearance of tuberculosis, ZN stain peculiarities and caveats and all the scientific rigors of method validations. The proposed project director, Prof dr Sabina Zurac, has more than 25 years of experience in pathology, 23 of them in a hospital diagnosing many cases of infectious diseases with confounding and treacherous histopathologic appearances due to superimposing of different pathogens (tuberculosis, HIV infections, hepatitis viruses B, C and D infections, leprosy, different opportunistic infections such as cryptococcosis, coccidioidomycosis, candidosis etc). Moreover, Prof dr Sabina Zurac was author / co-author in different publications and presentations concerning different infectious pathogens, tuberculosis included (see Table1).

Table 1. Selected list of publications / presentations - infectious diseases (impact factor IF)

1. Jugulete G, […], Zurac S, et al. Severe form of A1H1 influenza in a child - case presentation. Rom J of Legal Med. 2018; 26: 387-391. IF 0,483.
2. Boda D, [...], Zurac S, et al. Human papilloma virus: Apprehending the link with carcinogenesis and unveiling new research avenues Int J Oncol. 2018 Mar;52(3):637-655. doi: 10.3892/ijo.2018.4256. IF 3.571
3. Boda D, [...], Zurac S et al. HPV strain distribution in patients with genital warts in a female population sample. Oncol Lett. 2016 Sep;12(3):1779-1782. IF 1.390
4.S. Zurac, et al, Natural killer cells in HIV infection. 26th ECP. Virchows Archiv, 2014;465, Supplement 1:334
11.Staniceanu F, [...], Zurac S, et al. Macrophages in children: They do not impact AIDS progression more than CD4+ T cells. 25th ECP. Virchows Arch (2013) 463:224
5. Stăniceanu F, Nichita L, Zurac S et al. The Importance of Autopsy in HIV Infected Patients Virchows Archiv (2012) 461 (Suppl 1): S331-S332. ISSN 0945-6317
6. Nichita L, Zurac S et al. Dendritic cells- HIV: early interactions. Rom J Intern Med. 2011;49(4):251-5.
7. Staniceanu F, Zurac S et al. Pathologic aspects in AH1N1 virus-related deaths in Romania. 3rd Intercongress of European Society of Pathology, Krakow, Poland, 2010, Virchow Arch 2010; 457:278-279
8.Staniceanu F [...] Zurac S et al. Pulmonary lesions in 97 fatal cases of pandemic AH1N1 viral infections in Romania. The 28th Congress of International Academy of Pathology (IAP), Sao Paolo, Histopathology, 2010; 57:174
9.Zurac S.A et al. Chronic hepatitis with dual B and C hepatitis viruses infection: particularities of the histopathologic appearance. 22nd European Congress of Pathology (ECP), Florence, Italy. Virchows Arch (2009) 455 (Suppl 1):S413
10.Staniceanu F, Zurac S et al. Opportunistic infections in HIV+/AIDS patients – comparative autopsy study (21th ECP, Istanbul, September 2007) Virch Arch 2007; 451: 433
11. Zurac S et al Histopathologic particularities of Hepatitis D virus chronic hepatitis (the 20th ECP, Paris, September 2005) Virchows Archiv 2005, vol 447, nr.2, p303
12.Staniceanu F, [...],Zurac S. Tuberculous meningitis in adulthood; an autopsy study (19th ECP, Lubljana, Slovenia, September 6-11, 2003) Virchows Archiv 2003, 443, 2, p426-427
13.Staniceanu F, Streinu Cercel A, Zurac S. Frequency of the opportunistic infections in HIV-infected persons; autopsy findings (XXIV International Congress of the IAP, Amsterdam), Histopathology, 2002, 41, p196
14.Staniceanu F, Zurac S, Streinu Cercel A. Rabies in Romania – epidemiology and two human cases: autopsies report (18th ECP, Berlin, Germany) Virchows Archiv 2001, vol 439, nr.3, p 474
15.Ardeleanu C, Zurac S, et al, [CUTANEOUS LEISHMANIASIS – DIFFERENTIAL DIAGNOSTIC PROBLEMS] (Therapeutics, pharmacology and clinical toxicology; 2005.4, 99-103)
16.Staniceanu F, Zurac S, Streinu-Cercel A. [ASPERGILLOSIS IN HIV INFECTED PATIENTS] (Therapeutics, pharmacology and clinical toxicology 2002,3,56-58)
17.Ardeleanu C, Zurac S et al. [COCCIDIOIDOMYCOSIS IN HIV INFECTED PATIENTS] (Therapeutics, pharmacology and clinical toxicology; 2005;3:58-60)
18.Staniceanu F, Zurac S, Streinu-Cercel A. [CRYPTOCOCCOSIS IN HIV INFECTED PATIENTS] (Therapeutics, pharmacology and clinical toxicology 2002,3,60-62)
19.Staniceanu F, Zurac S, Streinu-Cercel A. [PNEUMOCYSTOSIS IN HIV INFECTED PATIENTS] (Therapeutics, pharmacology and clinical toxicology 2002,3,63-66)
20.Staniceanu F, Zurac S, Streinu-Cercel A. [CMV INFECTION IN HIV INFECTED PATIENTS] (Therapeutics, pharmacology and clinical toxicology 2002, 3,67-69)

Also, Prof dr Sabina Zurac has paramount expertise in performing and analyzing special stains and immunohistochemical tests, both categories being prone to false positive and negative results. Prof dr Sabina Zurac organized and managed the Immunohistochemical Compartment in the Department of Pathology from Colentina University Hospital since 2007 and has considerable expertise in interpreting immunohistochemical parameters, the results being acknowledged by publications of scientific papers and presentations in national&international congresses (see Table 2).

Table 2. Selected list of publications / presentations of immunohistochemical studies

1.Neagu M, [...], Zurac S. Inflammation: A key process in skin tumorigenesis. Oncol Lett. 2019 May;17(5):4068-4084. doi: 10.3892/ol.2018.9735. IF 2018: 1.871. Main author
2.Solomon I, [...], Zurac S. The impact of lifestyle factors on evolution of atopic dermatitis: An alternative approach. Exp Ther Med. 2019 Feb;17(2):1078-1084. doi: 10.3892/etm.2018.6980. IF 2018 1.448 Main author
3.Bucur M, [...], Zurac S, Ionescu E. Variation in Expression of Inflammation-Related Signaling Molecules with Profibrotic and Antifibrotic Effects in Cutaneous and Oral Mucosa Scars. J Immunol Res. 2018 Nov 28;2018:5196023. doi: 10.1155/2018/5196023. IF 3,404 Main author
4.Brînzea A, [...], Zurac SA, Ion DA. TIMPs expression in lentigo maligna÷lentigo maligna melanoma versus aged skin - a review of the literature and personal experience. Rom J Morphol Embryol. 2017;58(3):717-721.

5.Turcu G, [...], Zurac SA. CEACAM1: Expression and Role in Melanocyte Transformation. Dis Markers. 2016;2016:9406319. doi: 10.1155/2016/9406319. IF 2.348. Main author
6.Zurac S et al. Variations in the expression of TIMP1, TIMP2 and TIMP3 in cutaneous melanoma with regression and their possible function as prognostic predictors. Oncol Lett. 2016 May;11(5):3354-3360. IF 1.390 Main author
7.Gradinaru S, [...], Zurac S, et al. Repair of the Orbital Wall Fractures in Rabbit Animal Model Using Nanostructured Hydroxyapatite-Based Implant. Nanomaterials 2016, 6, 11; doi:10.3390/nano6010011 IF 1.48 Main author
8.Filimon A, Zurac SA et al. Value of dopachrome tautomerase detection in the assessment of melanocytic tumors. Melanoma Res. 2014 Jun;24(3):219-36. IF 2.518 Main author
9.Alexandru A, Zurac S et al. Direct immunofluorescence on hair follicles-present and future perspectives. Am J Dermatopathol. 2013 Jun;35(4):472-6. IF 1.418 Main author

She also participated / managed research project dedicated to organization of a histopathology laboratory and respectively a morgue department were she combined research&development, with teaching and diagnostics. Her expertise permitted the development of a modern infrastructure of a Department of Pathology combining the teams of pathologists and researchers (both with academic and nonacademic affiliation) from three reputed medical institutions with solid research background: Colentina University Hospital, University of Medicine and Pharmacy Carol Davila and National Institute of Infectious Diseases Matei Bals, Bucharest. In the pandemic of Sars-Cov2 infection she was the first pathologist to perform autopsies to establish the pathological background of the infection and she actively collaborates with Prof Martin Lammens, dept of Pathology, Antwerp University Hospital. Also she is now conducting a project of institutional development enhancing dermatooncology and dermatopathology infrastructure and research (see Table 3).

Table 3. List of infrastructure projects.

1. Project director " Multi-disciplinary platform for regional institutional capacity enhancing in dermatooncology and dermato-pathology domains. [PATHDERM]". 61PCCDI / 2018. 2018-2021. UEFISCDI 5,287,148 lei (1,137,021.07 EUR / 1EUR = 4.65 Lei) http://cdpcolentina.ro/buton11pathderm.html
2. project responsible in ["Modernization and sustainability of the research development and innovation infrastructure of a MORGUE DEPARTMENT with research development, teaching and diagnostic profile"] National Plan of research development and innovation II 193/CP/I/09.09.2008, 2008-2010. Coordinator National Institute of Infectious Diseases Matei Bals, partners UMF Carol Davila; Colentina University Hospital
3. researcher in ["Modernization and sustainability of the research development and innovation infrastructure of a DEPARTMENT OF PATHOLOGY with research development, teaching and diagnostic profile"] National Plan of RDI II 136/CP/I/19.09.2007, 2007-2009. Coordinator UMF Carol Davila, partner Colentina University Hospital

She also was key expert in another project ("Image-Based Assisted Diagnosis and Prognosis of Cutaneous Melanocytic Tumors" PN-II-RU-TE-2011-3-0249) aiming to develop novel computed image-based methods for the detection, analysis, quantification, and classification of melanocytic tumors for diagnosis and prognosis by using medial axes models and techniques; the fractal dimensions of specific medical images and the relation between the fractal dimension of a shape and its medial axis were studied. Basically, we developed new shape extraction and quantification techniques for the basic morphological and geometrical properties identified as relevant for the benign/malignant nature of the melanocytic tumors by dermatologists&pathologists; thus, we developed new classification techniques able to detect biologic character of melanocytic tumors.

B2. Curriculum vitae (maximum 2 pages)

This must contain at least the following categories of information:

a) information about the degrees and diplomas;

- Certificate in Management of Health Services 2019
- Master in Management of public health and health services 2012
- PhD degree since May 2005 with thesis "Hepatic lesions in postviral chronic hepatitis according to the type of the hepatitic virus involved in the etiology of the disease", "Carol Davila" University of Medicine and Pharmacy Bucharest, Romania
- senior pathologist since 2003, pathologist since 1998
- MD degree since 1994, "Carol Davila" University of Medicine and Pharmacy Bucharest, Romania, Faculty of General Medicine

b) information about the professional experience and jobs. This will include, in particular, the professional positions where the project leader coordinated a team, a group or a research laboratory.

- Professor (since 2015), associate professor (since 2009), lecturer (since 2006) Faculty of Dental Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; duties: teaching and research activities; fields of interest: infectious diseases, inflammation, dermato-pathology, oral pathology, cancer biology; managing activities: coordination of the Department of Pathology (chair head) since 2011
- Senior pathologist (since 2004), pathologist (since 1999), resident in pathology (since 1998) in Department of Pathology, Colentina University Hospital, Bucharest, Romania; duties: diagnostic and research activities; managing activities: coordination of the Department of Pathology since 2011, coordination of the compartment of Immunohistochemistry 2007-2011.
- pathologist/ resident in pathology (1998-1999) in National Institute of Infectious Diseases Matei Bals, Bucharest. duties: diagnostic and research activities
- Resident in pathology (1995-1998), Fundeni Clinical Institute, Bucharest, Romania
- Pathologist, fellow in oral pathology Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands; duties: diagnostic and research activities; 2005-2006

c) scientometric indicators: Hirsch index and the total number of citations (without self-citations), according to Web of Science, for the research areas where these indicators are relevant;

- H-index 10; 360 citations (without self-citations) (Web of Science core collection); H-index 11; 441 citations (without self-citations) (Web of Science all data bases, Clarivate Analytics)

d) at least one the profile address from Scopus Author ID, ORCID, Researcher ID, Google Scholar or MR Author ID;

Google Scholar – Sabina Zurac Profile

ORCID ID: https://orcid.org/0000-0002-3498-8454

e) the profile address from www.brainmap.ro.

UEFISCDI ID (UEF-iD) in BrainMap: U-1700-038T-9448

B3. Defining elements of the remarkable scientific achievements of the project leader (max. 4 pages)

B3.1 The list of the most important scientific publications from 2012-2020 period.

For natural sciences, exact sciences, engineering sciences and social sciences: Please indicate the most relevant papers of the project leader (maximum 10) including:

• Articles: Please point out the most relevant articles published by the project leader. Please indicate the articles accepted for publication, with the mention of the date of acceptance. The evaluation will focus on the articles where the project leader is a main author, but in the situation when there are papers published as a co-author, which are considered relevant for his/her scientific production by the project leader, these can be indicated. The format is as follows:

Identification data:	Bucur M, […], **Zurac** S, Ionescu E. Variation in Expression of Inflammation-Related Signaling Molecules with Profibrotic and Antifibrotic Effects in Cutaneous and Oral Mucosa Scars. J Immunol Res. 2018 Nov 28;2018:5196023.
Is he/she a main author?	YES
Is it in the project's field?	YES
Number of citations:	1
DOI (Digital Object Identifier)	10.1155/2018/5196023

Identification data:	Turcu G […] **Zurac** S CEACAM1: Expression and Role in Melanocyte Transformation. Dis Markers. 2016;2016:9406319.
Is he/she a main author?	YES
Is it in the project's field?	YES
Number of citations:	4
DOI (Digital Object Identifier)	10.1155/2016/9406319

Identification data:	Gradinaru S, […], **Zurac** S, […]. Repair of the Orbital Wall Fractures in Rabbit Animal Model Using Nanostructured Hydroxyapatite-Based Implant. Nanomaterials 2016, 6, 11
Is he/she a main author?	YES
Is it in the project's field?	YES
Number of citations:	1
DOI (Digital Object Identifier)	10.3390/nano6010011

Identification data:	Filimon A, **Zurac** SA, […], Negroiu G. Value of dopachrome tautomerase detection in the assessment of melanocytic tumors. Melanoma Res. 2014 Jun;24(3):219-36.
Is he/she a main author?	YES
Is it in the project's field?	YES
Number of citations:	4
DOI (Digital Object Identifier)	10.1097/CMR.0000000000000066

Identification data:	Ionescu AM, […], **Zurac** S. In vivo Diagnosis of Primary

	Cutaneous Amyloidosis -the Role of Reflectance Confocal Microscopy. Diagnostics (Basel). 2019 Jun 27;9(3). pii: E66.
Is he/she a main author?	YES
Is it in the project's field?	YES
Number of citations:	1
DOI (Digital Object Identifier)	10.3390/diagnostics9030066

Identification data:	Neagu M, […] **Zurac** S. Inflammation: A key process in skin tumorigenesis. Oncol Lett. 2019 May;17(5):4068-4084.
Is he/she a main author?	YES
Is it in the project's field?	YES
Number of citations:	12
DOI (Digital Object Identifier)	10.3892/ol.2018.9735

Identification data:	Solomon I, […], **Zurac** S. The impact of lifestyle factors on evolution of atopic dermatitis: An alternative approach. Exp Ther Med. 2019 Feb;17(2):1078-1084.
Is he/she a main author?	YES
Is it in the project's field?	YES
Number of citations:	3
DOI (Digital Object Identifier)	10.3892/etm.2018.6980

Identification data:	**Zurac** S, […], Tsatsakis AM. Variations in the expression of TIMP1, TIMP2 and TIMP3 in cutaneous melanoma with regression and their possible function as prognostic predictors. Oncol Lett. 2016 May;11(5):3354-3360
Is he/she a main author?	YES
Is it in the project's field?	YES
Number of citations:	35
DOI (Digital Object Identifier)	10.3892/ol.2016.4391

- **Monographs**: -
- **Patents**: Please indicate the patents/utility models with a technologic transfer obtained in other countries of the European Union or in member countries of OECD. The format is as follows:

Identification data:	Constantin C, Neagu M, Marinescu B, **Zurac** S. Tumour cell clone obtained from chemically induced murine carcinogenesis model. RO131985-A0/2017
The issuer office of patent	OSIM, Romania
Is it in the project's field?	YES

Identification data:	Filimon A, Ghenea S, Negroiu G, Petrescu S M, Sima E, Staniceanu F, **Zurac** S. Human polyclonal anti-dopachrome tautomerase antibody. RO123570-B1/ 2013
The issuer office of patent	OSIM, Romania

Is it in the project's field?	YES

At most 3 significant works for the activity of the project leader can be uploaded on the web platform in electronic format.

B3.2. The autonomy and visibility of the scientific activity. Please indicate a number of maximum 5 factual arguments of the high degree of autonomy and international visibility of the research activity developed by the project leader. The arguments can belong to one ore more of the following categories, but not necessarily from all categories:

(1) fundraising by research projects (academic grants or contracts with the industry) where the project leader was the main investigator (PI) or project coordinator; for each project will be given the following concise information: title, funding agency, total amount in euros and the ongoing period (if the information is available)

1. Project director "Multi-disciplinary platform for regional institutional capacity enhancing in dermatooncology and dermato-pathology domains. [PATHDERM]". 61PCCDI / 2018. 2018-2021. UEFISCDI 5,287,148 lei (1,137,021.07 EUR / 1EUR = 4.65 Lei)
http://cdpcolentina.ro/buton11pathderm.html
- 44 articles in ISI indexed medical journals, 3 BDI indexed journals, 52 presentations at national / international congresses, one book chapter in an international publishing house

2. Project director "Regression-based theranostic polyfactorial classifier for melanoma patients stratification. (MELTAG)". 190/2014; 2014-2017. UEFISCDI financing 1,250,000 lei (283,446.71 EUR / 1EUR = 4.41 Lei) http://www.cdpcolentina.ro/01%20meltag.html
- 15 articles in ISI indexed medical journals, 1 article in BDI indexed journals, 14 presentations at national / international congresses, 7 book chapters in international publishing houses, 1 patent

3.Postdoctoral Program POSDRU / 89 / 1.5 / S / 60746 Cellular and molecular biologies with applications in medicine. Institute of Biochemistry of the Romanian Academy. „Mechanisms involved in tumor regression in melanoma; corroboration with prognostic factors and disease progression". 2011-29013. POSDRU financing, 24,000EUR.
http://postdoc.biochim.ro/bcm/people/postdocs.php
- 2 articles in ISI indexed medical journals, 3 articles in BDI indexed journals, 5 presentations at national / international congresses.

(2) the management of the research activity by establishing and/or running some research teams or work groups which had as a result outstanding scientific achievements (referring to B1 and/or B3.1 and/or other B3.2 sections);

1. key expert in „Identifying the presence of Helicobacter Pylori in histopathological slides with artificial intelligence. Pilot Project", Project coordinator: Innovative Media Production SRL; partner

Colentina University Hospital, Bucharest, Romania. 2020-2021. Personal contributions from each institutions: 302,393 lei (62,998.54 EUR / 1EUR = 4.8 Lei). https://www.zaya.ai/

2. Establishing and managing the research team of the Department of Pathology of Colentina University Hospital, Bucharest, Romania with results in more than 100 papers in ISI indexed medical journals, more 200 papers in BDI / CNCSIS B + indexed journals, more than 2,000 presentations at national / international congresses

3. Vice-Dean for Scientific Problems / Research of Faculty of Dental Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania. "Carol Davila" UMF has position 201-300 in the field of Clinical Medicine (Shanghai ARWU classification).

(3) the most important international prizes: silver medal in 2nd Balkan Olympiad of Chemistry, Sofia, Bulgaria, 1988, gold medal in the 20th International Olympiad of Chemistry, 1988, Helsinki

(4) the status of invited speaker to prestige universities

1. Stefan O, [...], Zurac SA, E-cadherin and N-cadherin expression pattern in common melanocytic nevi, European Congress of Pathology, Lyon, France, 2019

2. Tudor G, [...], Zurac SA, Intravascular nevus cell protrusion and aggregates in otherwise common melanocytic nevi, European Congress of Pathology, Lyon, France, 2019

3. Zurac S et al. Histopathologic diagnosis of mycosis fungoides - how much histopathology is really involved? Spring Symposium, European Academy of Dermatovenerology, Cracow 2013

4.Zurac S et al Matrix metalloproteinases underexpression in melanoma with regression European Congress of Pathology, Prague, Cehia, 2012

5.Bastian A, [...], Zurac S et al. Tyrosinase and TRP2 expression in hipomelanotic malignant melanoma, the III Intercontinental Congress of Pathology, Bacelona, Spain, 2008

(5) the status of a member of commission of doctorate candidate at prestige universities[3]

Member of commission of doctorate canditate for 8 candidates at "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania (position 201-300 in the field of Clinical Medicine (Shanghai ARWU classification)).

(6) the status of member in the editorial board of the ISI Web of Science journals having the article influence score at least 0.5. Lead Guest Editor for the Special Issue "Mesenchymal Changes in Tumorigenesis and Tumor Progression" Analytical Cellular Pathology, 2019, IF 1.788

C. Description of the research project *(maximum 10 pages)*

C1. *Topics (issues).* C1.1 The importance of the problem to be addressed from a scientific, technological, socio-economic or cultural point of view

Modern medicine, irrespective of the specialty, involves daily interactions with a huge volume of information, with more and more time-consuming browsing and analysis of them. In various fields, artificial intelligence (AI) software is being developed, such as interpreting MRI lesions in Parkinson disease[1], interpreting breast lesions[2], or even developing a personalized medication[3]. The utility of artificial intelligence models in pathology is unquestionable, beginning with the pathologists' unique expertise in recognizing & interpreting various morphological, histochemical, immunohistochemical and genetic lesions and their consequent assembly in a diagnostic. The most successful deep learning algorithms developed so far are based on the principle of image recognition, a task that can be divided into three main categories: detection (absence or presence of abnormalities or pathology in an image), classification (prediction of image regions' properties, such as malignant vs. benign), and segmentation (isolate structures, enabling volume measurements or calculation of other properties). These are all relatively simple single tasks and thus examples of medical AI, which means the software works only within a very limited context and cannot take on tasks beyond image recognition. We set out, for a start, to create an AI software that could identify the presence of bacilli on histopathological preparations with a high degree of certainty. We chose fast acid bacilli (FAB) on Ziehl Nielsen (ZN) stained histopathological preparations for this purpose. Tuberculosis (TB) is an infectious disease with ongoing increasing incidence worldwide, also in well-developed countries; FAB identification on histopathologic slides confirm the diagnosis, reducing the need of expensive and time consuming other method of investigations (such as PCR); however, due to technical difficulties combined with the paucity of the bacilli in a lesion, the pathologist is spending hours looking for one bacillus in 2-3-4 cm^2 of tissue. The help of AI in this endeavour would be priceless.

C1.2. The difficulties that may be encountered in addressing the topic proposed

AI has the power to transform our ability to see through this complexity and to create new highly integrated diagnostic signatures that provide an opportunity to fuse large data sets and provide insights that are not possible with the human eye or the human intellect alone. The challenge this facility will present will be to translate and apply the findings to practical, secure, and effective treatment options predictions, and accurate diagnostic and prognostic opinion. Several difficulties are encounter: a) **The access to large high-quality labelled datasets for training**. This is a task that we handle by Department of Pathology of Colentina University Hospital (CUH) that provide histopathological specimens and with WSI scanning software that provide necessary tools to acquire images to a proper quality level. b) Deep learning models will be trained on **simple 2D pictures**. In reality, microscopic examination use a fine tuning for image clarity that offers a 3rd dimensions,

deepness, with outmost importance when dealing with very thin structures, such as FAB. For specific images, consultation in panel will be performed. c) **Non-standardized acquisition of images** is one of the biggest challenges. If several persons acquire images with different setups of the scanner and camera, this should provide images with noise and a variety in image dataset. The more variety there is in the data, the larger the dataset needs to be to ensure the deep learning network results in a robust algorithm. A method to overcome this issue is to have a standardised procedure of scanning and quality control of image dataset. Another method to get over this barrier is to apply transfer learning, which is a pre-processing technique aimed to overcome scanner and acquisition specifics.

C1.3. The limitations of current approaches in the context of the state of the art in the field.

To date, some attempts were done in order to identify FAB in smears (sputum)[4] [5] [6] but no attention was delegate towards histopathologic slides (section of tissue from paraffin blocks). There is obvious increased difficulty in identifying FAB in tissue than in smears taken into account that smears permit full display of the bacilli while on tissue sections one can deal with fragments of the bacilli, depending on the cutting incidence. Moreover, the overall background in sputum is simpler than in tissue due to the complexity of tissue structures compared with the appearance of mucus or of several epithelial &inflammatory cells from sputum. Despite the technical difficulties, for health system is more useful to identify FAB in tissue (thus providing diagnosis) than their identification in sputum (method used in screening; diagnostic implication for clear cut positive results). False positive results in screening methods doesn't impede the value of investigation, people being latter subject of further medical investigation in order to establish proper diagnosis and treatment, while false positive result in a diagnostic method may have catastrophic consequences for patient's well-being.

C2. *Objectives*. The general principles of the scientific approach will be presented, underlining the following aspects: C2.1: the concrete objectives of the project;

Main objective: Creating an artificial intelligence software capable of identifying the presence of FAB on histopathological preparations

Secondary objectives: 1) Creating an online platform that allows remote identification of images photographed from histopathological preparations and 2) Creating a database with FAB images

C2.2 the elements of originality & innovation of the objectives in the context of the current state of the art in the field and in relation to the previous projects developed by the project leader.

We will use whole slide image (WSI) as a means of acquiring image data. In recent years, attempts have been made to capture the entire slide with a scanner and save it as a digital image (whole slide image). As far as we know this approach has not been used before in a study for finding the presence of bacilli in histopathological preparations. Starting from the above-mentioned originality element we have another two innovative aspects that goes into our study: ***quantity of the images*** from the dataset and the ***pre-processing of the WSI***. Given the use of WSI, we can ***acquire more images faster***

than any other previous study which used a maximum of a couple of hundreds of images. Thanks to WSI, we can have a couple of hundreds of images just from one WSI. Now it comes the pre-processing part that helps us to divide the WSI in local mini patches of 512x512. Overall, the use of WSI means more data than ever before and new ways of pre-processing. Using a mix of machine learning algorithms that have given the best results in previous studies in a manner that has never been done before is our way of bringing novelty in the creation of an AI software capable of identifying the presence of bacilli on histopathological preparations. The fifth and the last element of originality is represented by the ***development of an easy-to-use online platform*** for medical experts that allows for remote identification of images photographed from histopathological preparations.

C3. Impact. **C3.1 the potential to significantly advance the knowledge of the field, by introducing new concepts or approaches and by opening new areas or research directions**

In histopathology, the "next big thing" is not a new type of image delivery system, but technologies to improve or accelerate the interpretation of image data and facilitate/diminish pathologist's tasks. While machine learning uses algorithms to analyse data, learn from data and make informed decisions based on what it has learned, deep learning is a sub-field of machine learning based on multi-layered algorithms to create a "artificial neural network" that can learn and make smart decisions on its own. The recent "hype" about AI in histopathology is mainly due to the success of the deep learning tools for medical image analysis. Methods of deep learning-based pattern recognition are expected to advance the pathology field by integrating clinical, radiological, and genomic data to diagnose diseases accurately and predict patient prognoses. In the process, **AI is expected also to address the complexities and challenges of data integration across the full spectrum of medical data** (epidemiological, clinical, radiological, pathological, and genomic) that will **ultimately chart the course for patient therapy and clinical outcomes (personalized medicine)**[7].

C3.2. The potential impact of the project and/or of the applied research directions explored in the project (if applicable) on the scientific, social, economic or cultural environment.

Health care system impact: ***a) patient's level:*** One of AI 's major opportunities is to reduce fragmentation. Nonetheless, AI's additional success in enhanced workflows, diagnostic precision and predictive ability could be the ultimate driver of primary diagnostic AI adoption. Thus AI, if properly designed and incorporated, brings value as a discipline to pathology and patients. ***b) public health***: Our project aims to considerably improve the quality of the diagnosis of tuberculosis on paraffin embedded tissue. One should not treat easily the enormous effort (measured in time, ocular fatigue, awareness) deployed by a pathologist when examining a ZN stain; human error occurrence is very frequent. By increasing the accuracy of the diagnosis, especially by retrieving some paucibacillary cases easily missed by an overwhelmed pathologist, the rate of diagnosis will increase with subsequent proper treatment and implicitly diminishing of the number of people transmitting TB.

Thus, further steps will be taken towards TB eradication on national and international level. ***c) pathology***. The disruptive potential of deep learning and AI, certainly in histopathology, is both a lot of excitement and uneasiness. We regard deep learning as an excellent resident of histopathology, the more pictures that it analyses, the better it gets. Obermeyer& Emanuel predict that machine learning will produce big winners and losers in healthcare, with radiologists and pathologists among the biggest losers[8], not only but improving diagnostic accuracy but also by displacing much of the work of radiologists and pathologists. There is the dystopian argument that AI will extinguish all radiologists, as well as the delusional belief that AI and machines would merely assist pathologists and never replace them. Conclusion is that both sides are still matter of dabate.

Economic impact: ***a) general impact of AI in medicine***: Advances in computer vision, which is also relevant to medical imaging, have stirred interest among technology giants, venture capitalists, and governments. Healthcare was ranked as the most important area of AI start-up investments in 2017, due to the countless opportunities to leverage AI in its quest for more accurate, proactive and comprehensive patient care. As medical imaging is one of the fastest moving areas with changes in healthcare technology, the expectations are very high and have escalated into a real hype. ***b)particular impact of our project:*** the capacity of fast and accurate diagnosis of TB on histopathological slides will dramatically diminished the costs in supplementary investigations for the patient (imagistic investigations and molecular biology), precocious diagnosis (with subsequent 1. shorter and cheaper treatment for an uncomplicated disease and 2. cutting the risk of further transmission), faster recovery of the patient (lower number of days of medical leave, rapid economic reintegration of the patient).

Social impact: more patients with TB will be diagnosed and treated with obvious increase of quality of life both on individual and general level.

***C4. Methodology*. C4.1. the choice of the investigation methodologies and tools and their use to address the problem proposed in the context of the state-of-the art in the field;**

The high-level picture of our research methodology is described in Figure 1. Our research has 5 main components, which are detailed. The loops in the figure represent the continuous research process that we plan for iteratively refining several components, towards the best results for our dataset.

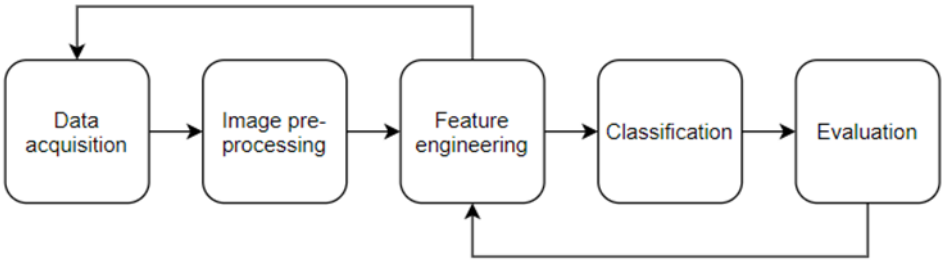


Figure 1: The research process of getting data, preprocessing, extracting features, classify, evaluation

1. Data acquisition: The most important aspect of our work is Data acquisition. Our plan is to use the following components: 10x20mm² slides, 40X magnification lens microscope, a camera (Basler acA2040-55uc), and the scanning software (Microvisioneer manual WSI)[9 10]. With these components and a procedure for scanning, we will be able to acquire new and precise data without much noise. Images used are taken from scanned ZN-stained microscopic samples, that consists of various categories (autofocused data, overlapping objects, single or few bacilli, views without bacilli, occluded bacilli, over-stained views with bacilli and artifacts). The input image layer will have an input size of 512x512 pixels with 3 channels RGB. Our acquisitions using this scanning tool will be high dimensional maps, which will be split into several images. We will use multiple data augmentation techniques, such as image rotation, reflection, and translation both for increasing the size of the dataset with less human effort but also to prevent overfitting in the classification process.

2. Image pre-processing: Nowadays, image pre-processing techniques have been widely used in computer vision methods to increase the performance of classification from multiple views: training or model evaluation performance, accuracy results, prevent overfitting, etc. In the following subsections, we describe a few of these techniques that we reviewed from literature. We mention only those that we think are relevant and could be used in our target problem**.**

2.1. Contrast Enhancement This technique is commonly used to get a clearer view of Tuberculosis Bacilli in pictures and eliminate undesired objects such as the bluish color of sputum or artifacts. We'll use both local and global Contrast Enhancement to improve the visualization of structure in both the darkest and lightest portions[11 12] as well a related technique, "Contrast Limited Adaptive Histogram Equalization" for clearance of purple reddish FAB[13 14].

2.3. Color space transformation and thresholding techniques. HSV space transformation was used for FAB detection[15]. Since FAB appears red-pink, the main concern in HSV model is the hue layer. In order to detect the pixels with properties of pink color, it is essential to get the chromatic information separated from the pixel intensity information. We will also use thresholding methods that improve the performance of the image processing algorithms such as Global thresholding for segmentation process of the FAB in ZN-stained smears in order to remove the tissues and background, Local Thresholding and Otsu Thresholding to overcome the brightness issues produced by the global thresholding technique in the processed images[16 17 18].

2.4. Morphological operations. For the object localization phase, different morphological operations, such as opening, closing, dilation, erosion, are used[15]. In the end, these techniques help in getting a binary output image with all FAB regions isolated. The scope of morphological operations in general is to fill out the holes and smoothen the edges of the objects. The process continues with an edge detection on the resultant image, minimizing the image and preserving the structural features. Resulting images are added together to form a single image with more enhanced boundaries.

2.5. Region Growing Method

Another technique that showed good results in detecting Tuberculosis Bacilli in images is used in the medical study[18]. The purpose of this method is to group pixels into some common regions taking into account the neighborhood of each pixel. The criteria of selection are based on the selected properties and pre-defined similarity (texture, brightness, and color or grey level of individual elements). The aim of the region-based segmentation method, in general, is to extract the homogeneous sectors from the given input image, i.e. to partition an image into regions.

3. Features engineering: After having pre-processed data, the next step is to create features for the classification task. Our plan is to use unsupervised machine learning algorithms to derive insights directly from data and prepare features for the supervised learning tasks since these models are more robust in deriving insights and features for the next tasks such as learning and classification. Unsupervised learning can be used as a pre-processing step for supervised learning tasks, since unsupervised learning of representation may allow better generalization of a classifier. Techniques for compression, dimensionality reduction, denoising, super-resolution have been proven to help machine learning methods in the medical field analysis. We divide these methods into classic-widely used methods and modern deep learning methods that gave the best results lately.

3.1. Classical methods in computer vision for features extraction: 3.1.1.Exploratory data analysis, such as Kernel Density Estimation (KDE) used for example to extract features from the spine image in the problem of Dendritic Spine Classification[19]. 3.1.2 Dimensionality Reduction, such as Principal Component Analysis (PCA) and clustering methods. In medical image analysis, these were used to obtain an unsupervised deep learning illumination invariant kernel PCA. Then, this kernel is used to obtain a low - dimensional embedding from X-ray fluoroscopy[20]. 3.1.3 Visio for features extraction: Techniques such as mean, variance and standard deviation of RGB color, HIS color space are used to get features from medical images like correlation, energy, contrast, homogeneity, and entropy features[21]. These features are then used to improve segmentation method performance. With a similar purpose of extracting features from images and assigning weights for them, we will add investigatory techniques such as Neighbourhood Component Analysis (NCA)[22] and Relief Analysis[23].

3.2. Deep Learning methods for features extraction: 3.2.1. Autoencoders: Stacked denoising autoencoders and Convolutional autoencoders to detect nuclei on breast cancer in digital histopathological images[24], to decode/encode nuclei and feature extraction from tissue section images[25], and to classify tissues and help histogram matching classification using images[26].3.2.2. Deep Boltzmann machines (DBM) for image processing by patches selection from the input images dataset[27] [28]. 3.2.3. Generative Adversarial Network (GAN) to improve the performance of medical image analysis by generating precise segments in retinal images as a stage in the pipeline of a supervised learning method[29] [30] [31].

4. Classification: we plan to apply first the state of the art methods, than to use a combination of these methods, such as combining classic methods with deep learning, and custom deep learning architectures. Several research and testing iterations, with customizing the previous steps will be use.

4.1 Classic machine learning method. We'll use machine learning techniques: Multilayer Perceptron (MLP), K-Nearest Neighbour (K-NN) and Support Vector Machine (SVM) to classify FAB in the segmented images[14]; to label the objects of interest (bacilli) in the segmented image, construct a vector with them, and then use it, for training and classification process of an SVM model[32]; to detect object of interest by Random forest models in a supervised learning classification pipeline[33].

4.2 Deep Learning Methods: We will first use the widely used concepts (and their variants) of Convolutional Neural Network (CNN), Faster Region-based Convolutional Neural Network (RCNN) with Region Proposal Networks (RPN), and Long short-term memory (LSTM) for implementation and evaluation of the classification methods for our target problem (find the bounding-boxes interesting objects in the input images and image classification) [27] [34] [35].

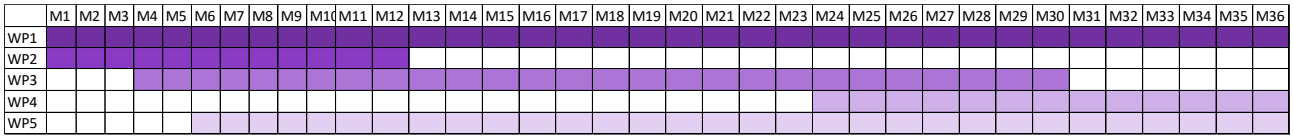
5. Evaluation: Apart from the statistical metrics used in the Computer Science field that we plan to use for evaluation using our dataset, we also plan to do a practical evaluation of our methods. We will acquire a new image dataset of (at least) 3000 pictures that is divided in 3 categories as follows: 1000 images dataset with positive diagnostic, 1000 images dataset with negative diagnostic, and 1000 images dataset with inconclusive diagnostic. All these images will not be used in the training process, to get a fair evaluation unseen data (in statistical terms this is equivalent to identify and prevent overfitting in the classification models that we iterate on). The target for our classification method is to obtain values for the common used metrics Accuracy, Precision and Recall above 95%.

C4.2 the design of the work plan and the timelines proposed in relation to the project objectives

Note: for personnel identification please check personnel list chapter C5.2.

Work package 1 (WP1)	*Management activities* **M1-M36. WP leader**: SZ. **Personnel:** SZ (0.5pm), AR (0.5pm), CiP (0.5pm), CM (0.5pm). **Purpose**: organization, coordination and management of the research and dissemination activities. **Methodology**: Project director (**PD**) SZ will chair the project management team (PMT) that includes WP leaders (SZ, AR, CiP, CM). Duties: organization & compiling minutes of PMT meetings and executing their decisions; signaling any contingencies in project execution to PMT; project financial administration; sending deliverables and reports to UEFISCDI within deadlines. **PMT** will meet twice a year and when needed; decisions will be approved by vote (in ties PD has decisive vote). PMT responsibilities: a) contractual matters; b) review of resource status and project progress; c) preparation of scientific&technical progress reports; d) approval of deliverables; e) ensure integration between results, deliverables and further achievements. **WP leaders** will coordinate WP activities. Responsibilities: a) develop the research design and the implementation guidelines; c) monitor and act as quality controller for the researchers work providing support when needed; d) compile the WP output in deliverables; e) coordinate report activity; f) monitor the ethical issues; k) monitor the compliance to the Intellectual Property Rights agreement. **Activities**: 1.1. Kick off meeting. 1.2-1.5. Monitoring and coordination of activities in the WP2-WP5. **Deliverables**: Kick off meeting report, annual meeting reports, annual financial and scientific and technical reports, final report.

Work package 2 (WP2)	*Development of an online platform to remotely identify images taken from histopathological specimens* **M1-M12. WP leader**: AR. **Personnel:** AR(1pm), AV(1pm), CC(0.5pm), SZ(2pm), CP(2pm), LN (2pm). **Purpose**: development of an online platform to remotely identify images taken from histopathological specimens. **Methodology:** Images online platform will be developed using SQL DB and PHP as backend software languages with a friendly HTML/CSS/JS frontend interface to easy access for visualisation and input diagnosis and comments on each image. **Activities**: 2.1 Scanning histopathologic ZN stained slides. Milestone: Mi1 acquisition of at least 3000 images during the period M1-M6. 2.2 Development of an online platform that allows remote identification of images taken from histopathological specimens. Deliverables: online platform for remote identification of images. Database of 20.000 histopathologic images. Annual RST report
Work package 3 (WP3)	*Development of an artificial intelligence software capable of identifying FAB*. **M3-M30 WP leader**: CiP. **Personnel:** CiP(6pm), SZ(1.75pm), CP(0.5pm), LN(0.5pm), CM(6pm), AR(4.25pm), AV(4.25pm), CC(2.5pm), BC(3pm). **Purpose**: Development of an AI software capable of FAB identification. **Methodology**: we will process the images from the data base by several consecutive methods: image pre-processing, segmentation (colour threshold, shape filtering and object detection), region growing method, feature extraction and feature selection, classification and model evaluation; as a continuous research process for iteratively refining several components until targeted results are obtained. **Activities**: 3.1 Scanning histopathologic ZN stained slides. Milestone: Mi2 acquisition of at least 9000 images until M12. 3.2 Image Pre-processing. 3.3 Feature engineering. 3.4. Classification. 3.5. Evaluation of models. **Deliverables**: AI software. Annual RST reports
Work package 4 (WP4)	*Validation of the FAB identifying AI software*. **M24-M36. WP leader**: CM. **Personnel:** CM(2PM), SZ(2pm), CP(2pm), LN(2pm), CiP(2pm), AR(1pm), AV(1pm), CC(1pm), BC(1pm). **Purpose**: Validation of the previously developed AI software for FAB identification. **Methodology**: AI software will be provided with 3 types of images: new images negative for PAB (1000), new images positive for FAB (1000) and 1000 debatable images selected as such by consensus of the 3 pathologists (SZ, CP, LN). Those images will be introduced into the image processing AI software. If the results do not match targeted accuracy, we get back into continuous research process loop for iteratively refining several components. **Activities**: 4.1 Scanning histopathologic ZN stained slides. Milestone: Mi3 acquisition of at least 3000 images until M26. 4.2 Refining components of image processing according with validation results Milestone: Mi4 Reach 95% accuracy of image diagnostic compared with pathologists' diagnosis. **Deliverables**: AI software. Annual RST report
Work package 5 (WP5)	*Dissemination* **M6-M36. WP leader**: SZ. **Personnel:** SZ(0.5pm), CP(0.5pm), LN(0.5pm), CM(0.5PM), CiP(0.5pm), CM(0.5pm), AR(0.5pm), AV(0.5pm), CC(0.5pm), BC(0.5pm). **Purpose**: Dissemination of the results of the research process. **Methodology**: All team members will have an active role in the dissemination activities. We have the responsibility to disseminate a full account of our research as broadly as possible, including, whenever applicable, negative findings and results. We will disseminate our findings by: a) Papers in international&national journals; b) Presentation in prestigious national & international symposia and congresses) Workshop with interested parties: SMEs, hospitals, universities, research institutions etc. **Activities**: 5.1-5.3. one presentation in a national /international congress /symposium and one paper in an indexed journal in the first year (5.1), second year (5.2) and third year (5.3). Milestones: Mi4 drafting an article in M9; Mi5 drafting an article in M18; Mi6 drafting an article in M30. **Deliverables**: 3 presentations; 3 scientific papers.



C4.3. the potential risks that may arise during the project implementation and the approaches proposed to mitigate them. The potential risks and their mitigations are listed in the table below:

Data management risk (low): Defectuous management of the enormous amount of data necessary for training and testing of AI. Mitigation strategy (MS): correct labeling of data and weekly storage.
Data quality risk (moderate): Insufficient technical quality of data (artifacts, image noise, beam hardening, partial voluming). MS: each slide will be evaluated by pathologist prior scanning; if the staining is deficient, another section will be cut from that paraffin block and another ZN stain will be performed. Further on we'll apply transfer learning (sub-field of machine learning that comprises techniques coping with certain differences between training and test data) as pre-processing technique aimed to overcome scanner and acquisition specifics. Robust methods of quality control will be used to asses the quality and completeness of training data to feed algorithms with high-quality information
Misdiagnosis risk (low): Debatable certainty of the data provided to AI. Histopathologic diagnosis is considered the gold standard; however, the quality depends on the professional level of the pathologist, being subject of human error. Mitigation strategy: each image will be evaluated in panel by two histopathologists; if consensus is not reached, the image will be excluded from the data set.
Risks of scientific dissemination: (low risk). If the Mi4, Mi5 and Mi6 benchmark (a draft article in M9, M18 and M30) are not reached, we will reallocate more workload to this end.
Financial risks (low): Mitigation strategy: planned periodically financial controls of the specific documentation by PMT; the existing research resources will be allocated to this project.
Risks associated with suppliers (low). Equipment and reagents providers have a stable international history and consistency in technical and operational efficiency.
Legislative risks (moderate). PD and WP leaders will monitor national and international law and will regularly assess the impact on its various objectives and activities.
Cyber-attacks risks (low). We will use encryption technology for storing&transferring medical imaging data; images will be stored on our own servers; personal patient data are not retain
Personnel risk (inability of the applicant to mobilize the necessary human resources) (low). The scientific and administrative staff planned to carry out this project is balanced in number&competence in order to fulfil the work plan. If staff migration occurs (resignations, training scholarships, personal problems) the institution has enough staff to take over the tasks provided in the project.
Environmental risks (low): the purpose, objectives &activities comply with all regulations regarding the disposal of bio-waste in the EU, therefore no negative impact on the environment is foreseen.
Institutional risk (low) - host institution has national importance (university hospital).

C5. *Resources and budget*. The existing, relevant infrastructure available for the project implementation will be described, as well as the novel equipment to be acquired.

CUH is a multidisciplinary hospital; the department of pathology includes in the research core the laboratories within CDPC (https://erris.gov.ro/Anatomo-Pathology) with modern equipment for the processing of biological samples for routine&complex histopathologic investigations (IHC, IFD, FISH/CISH, electron microscopy); within SCC operate the PATHUNIT&PATHOPLUS laboratories realized in partnership by CUH, University of Medicine and Pharmacy and Institute of Infectious Diseases Matei Balș Bucharest (access granted by a firm inter-institutional collaboration agreement. (http: //www.mateibals.ro/VIASAN/ServiciulProsectura/eng/echipamente.html, http://www.spitalul colentina.ro/anatomie-patologica/en/buton-en2.html). Very recently CUH acquired a manualWSI software for scanning specimens. We will to acquire a Deep Learning Workstation with 4 GPUs, 4x RTX 2080 Ti, Intel i9-9820X (10 Cores), 64 GB Memory, 2 TB NVMe SSD; costs: aprox 8500 eur.

C5.1 The time allocated to the project by each member of the project team, in person months

Sabina Zurac (SZ) PD, professor of pathology, senior pathologist, high expertise in infectious disease diagnosis. 7-person month (PM)**. Cristiana Popp (CP)** senior pathologist, high expertise in infectious disease diagnosis. 5 PM**, Luciana Nichita (LN)** lecturer**,** senior pathologist, high expertise in infectious disease diagnosis, 5 PM**, Ciprian Paduraru (CiP)** lecturer. PhD in Computer Science, high expertise in Machine Learning&Computer Vision 9PM, **Cristian Mogodici (CM)** expertise in Machine Learning&Computer Vision 9PM, **Alin Rauta (AR)** expertise in Machine Learning&Computer Vision 7PM, **Andrei Voicu (AV)** expertise in Machine Learning&Computer Vision 7PM, **Ciprian Ceausescu (CC)** expertise in Machine Learning&Computer Vision 5PM, **Bogdan Ceachi (BC)** expertise in Machine Learning&Computer Vision 5PM.

C5.2 The suitability of the project team and the research infrastructure

The team members, both doctors and software engineers have the necessary training as well as a vast experience in their field of expertise. The histopathological diagnosis is exclusively within the competence of the medical team of the Department of Pathology of CUH as excellence center nation-wide. PD (SZ), professor of pathology and senior pathologist, has a high experience in the management of other research projects and a vast activity of research and publication of specialized scientific articles. The team of software engineers has a high training in machine learning, deep learning and computer vision techniques with notable results in implementation on various other projects. The Department of Pathology of CUH has a large archive including numerous cases of TB with ZN slides to be used for microscopic scanning using the camera and WSI scanning software. This will result in a wide base of images that will be used in training and testing AI software. Also, CUH has a fully equipped laboratory for histopathologic processing and analysis.

C5.3 new equipment of great value (over 60.000 lei, VAT included) - not necessarily

C5.4 the budget breakdown per category of expenses/ year.

Budget Breakdown (lei)/year

Category of expenses	2021 (lei)	2022 (lei)	2023 (lei)	Total (lei)
Personnel	265,000	252,826	145,870	663,696
Logistics	150,000	60,000	80,000	290,000
Travel	25,000	35,000	35,000	95,000
Overhead	60,000	52,174	39,130	151,304
Total	500,000	400,000	300,000	1,200,000

Budget Breakdown (EUR)/entire project

Category of expenses	Total budget 2021 – 2023 (EUR)
Personnel	138,270
Logistics	60,416.67
Travel	19,791.67
Overhead	31,521.67
Total	250,000.00

References

[1] Singh P. A neutrosophic-entropy based adaptive thresholding segmentation algorithm: A special application in MR images of Parkinson's disease. Artificial Intelligence in Medicine, 2020; 104: 101838 https://doi.org/10.1016/j.artmed.2020.101838

[2] Lamy JB et al. Explainable artificial intelligence for breast cancer: A visual case-based reasoning approach. Artificial Intelligence in Medicine, 2019; 94:42-53. https://doi.org/10.1016/j.artmed.2019.01.001

[3] Chunyua L et al. Characterizing the critical features when personalizing antihypertensive drugs using spectrum analysis and machine learning methods. Artificial Intelligence in Medicine, 2020; 104: 101841. https://doi.org/10.1016/j.artmed.2020.101841

[4] Rosli, Fatin & Mashor, Mohd & Noor, Siti. (2019). An Automated Intelligent Identification and Counting System Procedure for Tuberculosis. Journal of Physics: Conference Series. 1372. 012079. 10.1088/1742-6596/1372/1/012079. https://www.researchgate.net/publication/337451665_An_Automated_Intelligent_Identification_and_Counting_System_Procedure_for_Tuberculosis

[5] M. El-Melegy, D. Mohamed, T. ElMelegy and M. Abdelrahman, "Identification of Tuberculosis Bacilli in ZN-Stained Sputum Smear Images: A Deep Learning Approach," 2019 IEEE/CVF Conference on Computer Vision and Pattern Recognition Workshops (CVPRW), Long Beach, CA, USA, 2019, pp. 1131-1137, doi: 10.1109/CVPRW.2019.00147.

[6] Carpio, Christian & Dianderas, Erwin & Zimic, Mirko & Sheen, Patricia & Coronel, Jorge & Lavarello, Roberto & Kemper, Guillermo. (2019). An algorithm for detection of tuberculosis bacilli in Ziehl-Neelsen sputum smear images. International Journal of Electrical and Computer Engineering (IJECE). 9. 2968. 10.11591/ijece.v9i4.pp2968-2981.

[7]Obermeyer Z, Emanuel EJ. Predicting the Future - Big Data, Machine Learning, and Clinical Medicine. N Engl J Med. 2016 Sep 29;375(13):1216-9. doi: 10.1056/NEJMp1606181. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5070532/

[8] Obermeyer Z, Emanuel EJ. Predicting the Future - Big Data, Machine Learning, and Clinical Medicine. N Engl J Med. 2016 Sep 29;375(13):1216-9. doi: 10.1056/NEJMp1606181. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5070532/

[9] https://www.baslerweb.com/en/products/cameras/area-scan-cameras/ace/aca2040-55uc/

[10] https://sites.google.com/a/microvisioneer.com/manual-wsi/home

[11]Gupta, Shefali and Yadwinder Kaur. “Review of Different Local and Global Contrast Enhancement Techniques for a Digital Image.” *International Journal of Computer Applications* 100 (2014): 18-23.

[12]Q. Tian and L. D. Cohen, "Global and Local Contrast Adaptive Enhancement for Non-uniform Illumination Color Images," *2017 IEEE International Conference on Computer Vision Workshops (ICCVW)*, Venice, 2017, pp. 3023-3030, doi: 10.1109/ICCVW.2017.357.

[13] Singh, Brij B. and Shailendra Patel. “Efficient Medical Image Enhancement using CLAHE Enhancement and Wavelet Fusion.” *International Journal of Computer Applications* 167(2017): 1-5

[14] Rosli, Fatin & Mashor, Mohd & Noor, Siti. (2019). An Automated Intelligent Identification and Counting System Procedure for Tuberculosis. Journal of Physics: Conference Series. 1372. 012079. 10.1088/1742-6596/1372/1/012079.

[15]S. R. Reshma and T. R. Beegum, "Microscope image processing for TB diagnosis using shape features and ellipse fitting," *2017 IEEE International Conference on Signal Processing, Informatics, Communication and Energy Systems (SPICES)*, Kollam, 2017, pp. 1-7, doi: 10.1109/SPICES.2017.8091342

[16] Anusha Linda Kostka J.E. (2019) A Review of the Medical Image Segmentation Algorithms. In: Peng SL., Dey N., Bundele M. (eds) Computing and Network Sustainability. Lecture Notes in Networks and Systems, vol 75. Springer, Singapore.

[17] Bangare, Sunil & Dubal, Amruta & Bangare, Pallavi & Patil, Suhas. (2015). Reviewing otsu's method for image thresholding. International Journal of Applied Engineering Research. 10. 21777-21783.
[18] M S, Mallikarjunaswamy & B., Rachna. (2013). Detection of Tuberculosis Bacilli using Image Processing Techniques. International Journal of Soft Computing and Engineering. 3. 47-51.
[19] Ghani MU, Mesadi F, Kanık SD, et al. Dendritic spine classification using shape and appearance features based on two-photon microscopy. *J Neurosci Methods*. 2017;279:13-21. doi:10.1016/j.jneumeth.2016.12.006.
[20] Fischer, Peter & Pohl, Thomas & Faranesh, Anthony & Maier, Andreas & Hornegger, Joachim. (2016). Unsupervised Learning for Robust Respiratory Signal Estimation From X-Ray Fluoroscopy. IEEE transactions on medical imaging. PP. 10.1109/TMI.2016.2609888
[21] Khutlang R, Krishnan S, Dendere R, et al. Classification of Mycobacterium tuberculosis in images of ZN-stained sputum smears. *IEEE Trans Inf Technol Biomed*. 2010;14(4):949-957. doi:10.1109/TITB.2009.2028339.
[22] Yang, Wei & Wang, Kuanquan & Zuo, Wangmeng. (2012). Neighborhood Component Feature Selection for High-Dimensional Data. JCP. 7. 161-168. 10.4304/jcp.7.1.161-168
[23] Zatzarinni, Rony & Tal, Ayellet & Shamir, Ariel. (2009). Relief Analysis and Extraction. ACM Trans. Graph.. 28. 10.1145/1661412.1618482.
[24]Xu, J., Xiang, L., Liu, Q., Gilmore, H., Wu, J., Tang, J., Madabhushi, A. (2016). Stacked sparse autoencoder (SSAE) for nuclei detection on breast cancer histopathology images. IEEE Trans. Med. Imaging 35, 119– 130. https://doi.org/10.1109/TMI.2015.2458702
[25] Hou, L., Nguyen, V., Kanevsky, A. B., Samaras, D., Kurc, T. M., Zhao, T., ... & Saltz, J. H. (2019). Sparse Autoencoder for Unsupervised Nucleus Detection and Representation in Histopathology Images. Pattern Recognition, 86: 188-200. https://doi.org/10.1016/j.patcog.2018.09.007
[26] Janowczyk, A. , Basavanhally, A. , Madabhushi, A. (2017). Stain normalization using sparse autoencoders (STANOSA): application to digital pathology. Comput. Med. Imaging Graph 57, 50–61. https://doi.org/10.1016/j.compmedimag.2016.05.003.
[27] Nahid AA, Mehrabi MA, Kong Y. Histopathological Breast Cancer Image Classification by Deep Neural Network Techniques Guided by Local Clustering. *Biomed Res Int*. 2018;2018:2362108. Published 2018 Mar 7. doi:10.1155/2018/2362108.
[28]Jeyaraj, P. R. and Nadar, E. R. S. , "Deep Boltzmann machine algorithm for accurate medical image analysis for classification of cancerous region," in *Cognitive Computation and Systems*, vol. 1, no. 3, pp. 85-90, 9 2019, doi: 10.1049/ccs.2019.0004.
[29] Shi Y, Cheng K, Liu Z. Hippocampal subfields segmentation in brain MR images using generative adversarial networks. Biomed Eng Online. 2019 Jan 21;18(1):5. doi: 10.1186/s12938-019-0623-8. PMID: 30665408; PMCID: PMC6341719.
[30] Iqbal, T., Ali, H. Generative Adversarial Network for Medical Images (MI-GAN) (2018) Journal of Medical Systems, 42 (11), art. no. 231. https://doi.org/10.1007/s10916-018-1072-9.
[31] Taeho Jo, Nho K, Saykin AJ. Deep Learning in Alzheimer's Disease: Diagnostic Classification and Prognostic Prediction Using Neuroimaging Data. *Front Aging Neurosci*. 2019;11:220. Published 2019 Aug 20. doi:10.3389/fnagi.2019.00220.
[32]Carpio, Christian & Dianderas, Erwin & Zimic, Mirko & Sheen, Patricia & Coronel, Jorge & Lavarello, Roberto & Kemper, Guillermo. (2019). An algorithm for detection of tuberculosis bacilli in Ziehl-Neelsen sputum smear images. International Journal of Electrical and Computer Engineering (IJECE). 9. 2968. 10.11591/ijece.v9i4.pp2968-2981.
[33] Nguyen D, Uhlmann V, Planchette AL, et al. Supervised learning to quantify amyloidosis in whole brains of an Alzheimer's disease mouse model acquired with optical projection tomography. *Biomed Opt Express*. 2019;10(6):3041-3060. Published 2019 May 28. doi:10.1364/BOE.10.003041
[34] Hosny A, Parmar C, Coroller TP, et al. Deep learning for lung cancer prognostication: A retrospective multi-cohort radiomics study. *PLoS Med*. 2018;15(11):e1002711. Published 2018 Nov 30. doi:10.1371/journal.pmed.1002711

[35] M. El-Melegy, D. Mohamed, T. ElMelegy and M. Abdelrahman, "Identification of Tuberculosis Bacilli in ZN-Stained Sputum Smear Images: A Deep Learning Approach," 2019 IEEE/CVF Conference on Computer Vision and Pattern Recognition Workshops (CVPRW), Long Beach, CA, USA, 2019, pp. 1131-1137, doi: 10.1109/CVPRW.2019.00147.