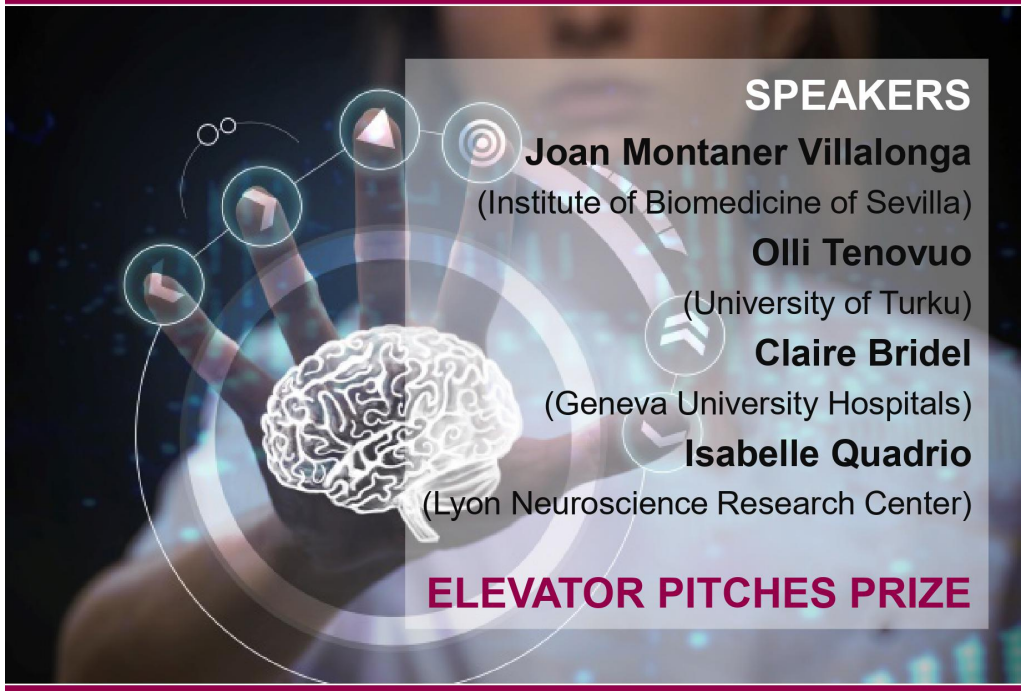
TRANSLATING BRAIN BIOMARKER RESEARCH TO CLINICAL PRACTICE: PROMISES AND PITFALLS

BIOMARKER DAY 2021
March 17, 2021
14:00-17:30 ONLINE

LECTURES
ELEVATOR PITCHES
ROUND TABLE



SPEAKERS

Joan Montaner Villalonga
(Institute of Biomedicine of Sevilla)

Olli Tenovuo
(University of Turku)

Claire Bridel
(Geneva University Hospitals)

Isabelle Quadrio
(Lyon Neuroscience Research Center)

ELEVATOR PITCHES PRIZE

FACULTÉ DE MÉDECINE
CENTRE FACULTAIRE D'INVESTIGATION TRANSLATIONNELLE EN BIOMARQUEURS (CITB)

UNIVERSITÉ DE GENÈVE

WELCOME

On behalf of the Organizing committee, we are delighted to invite you to the **Biomarker Day 2021** in a virtual format.

During the afternoon, we will have the chance to discover work of four experts about their recent research on biomarkers in different diseases: Stroke, Traumatic Brain Injury (TBI), Neuroinflammation and Neurodegeneration.

In addition, young investigators elevator pitches will be given.

To conclude the day, an interactive round table will take place with all regarding the problematic: "Why are we still failing to incorporate brain biomarkers into diagnostic guidelines for the biggest brain diseases?".

We are looking forward to seeing you online!

Jean-Charles Sanchez
Chair of the Biomarker Day 2021

PROGRAM OVERVIEW

14.00-14.10 **Welcome address**

Prof. FONTANA Pierre & Prof. SANCHEZ Jean-Charles (HUG & Faculty of Medicine, UNIGE)

STROKE

Oral presentation

14.10-14.35 **Using stroke biomarker in the field: triage or treat?**

Prof. MONTANER Joan (Institute of Biomedicine of Sevilla, Spain)

Elevator Pitch

14.35-14.40 **Blood biomarkers to detect atrial fibrillation as part of a primary stroke prevention strategy**

PALÀ Elena (Val d'Hebron Institute of Research, Barcelona, Spain)

14.40-14.45 **Blood biomarker panels for the early prediction of stroke-associated complications**

FAURA Júlia (Val d'Hebron Institute of Research, Barcelona, Spain)

14.45-14.50 **Alpha-1 antitrypsin as a biomarker for stroke prognosis**

RAMIRO Laura (Val d'Hebron Institute of Research, Barcelona, Spain)

14.50-14.55 **A panel comprising serum amyloid a, white blood cells and nihss for the triage of patients at low risk of post-stroke infection**

AZURMENDI Leire (Department of medicine, University of Geneva, Switzerland)

TRAUMATIC BRAIN INJURY

Oral presentation

14.55-15.20 **Biomarkers of traumatic brain injury - the biggest challenge of brain biomarker diagnostics?**

Prof. TENOVUO Olli (University of Turku, Finland)

Elevator Pitch

15.20-15.25 **Protein blood biomarkers in mild traumatic brain injury: CT triage at admission and outcome prediction**

CHIOLLAZ Anne-Cécile (Department of medicine, University of Geneva, Switzerland)

15.25-15.40 **Coffee Break**

NEUROINFLAMMATION

Oral presentation

15.40-16.05 **Fluid biomarkers in multiple sclerosis: hopes and reality**

Dr. BRIDEL Claire (HUG, Switzerland)

Elevator Pitch

16.05-16.10 **Glioblastoma biomarkers: in vivo syngeneic and PDX mouse models to identify potential biomarkers**

GUTIERREZ PELAZ Sara (Institute of Neuroscience of Castilla y León, University of Salamanca, Spain)

16.10-16.15 **Brain and Cardiac MR Image Reconstruction using Deep Learning**

ASLAM Ibtisam (HUG, Switzerland)

NEURODEGENERATION

Oral presentation

16.15-16.40 **Biomarkers for Neurodegenerative's diseases: where we stand, what's next?**

Dr. QUADRIO Isabelle (Lyon Neuroscience Research Center, France)

Elevator Pitch

16.40-16.45 **Concordance between brain imaging and fluid biomarkers in Alzheimer's disease: evidence from the Geneva cohort**

ALTOMARE Daniele (University of Geneva, Switzerland)

16.45-16.50 **Next generation biomarkers for the early diagnosis of Alzheimer's disease**

MOSSER Sebastien (PATIM, University of Geneva, Switzerland)

ROUND TABLE

16.50-17.35 **Why are we still failing to incorporate brain biomarkers into diagnostic guidelines for the biggest brain diseases?**

All speakers

17.35-17.40 **Closing remarks & price award**

Prof. SANCHEZ Jean-Charles & Prof. FONTANA Pierre (HUG & Faculty of Medicine, UNIGE)

ORAL PRESENTATIONS ABSTRACTS

MONTANER, Joan

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"Using stroke biomarkers in the field: Triage or treat?"

Joan Montaner, Neurovascular Research Laboratory, Vall d'Hebron Institute of Research (VHIR), Barcelona, Stroke Research Program, Institute of Biomedicine of Seville (IBIS), Department of Neurology, Hospital Universitario Virgen Macarena, Seville, Spain. Jmontaner-ibis@us.es

Our laboratory work focuses on the identification of biomarkers to be used as diagnostic and prognostic tools in ischemic and hemorrhagic stroke and also as companion diagnostics for several stroke therapies. Several experimental models of cerebral ischemia allow our lab to do screening of potential neuroprotectant compounds to be used as future stroke therapies that might be administered based on biomarkers information.

In the talk I will show recent data on a rapid POCT to be used at the ambulances to differentiate ischemic from hemorrhagic stroke and to select those ischemic strokes due to Large Vessel Occlusion (LVO). That technology might be used in the future to start reperfusion therapies outside of the hospitals in acute ischemic stroke patients or to shift the LVO patient to thrombectomy centers.

Beyond the acute phase, prediction of stroke outcome and the occurrence of post-stroke complications such as stroke-associated infections and assessment of stroke etiology to guide further studies or even therapeutic measures in cases of stroke of undetermined cause represent the main indications for the use of blood biomarkers in precision medicine.

I will discuss which of these medical indications is closer to the clinics and try to identify some of the reasons of the translational failure in the field of stroke biomarkers and how to break those barriers in the near future.

TENOVUO, Olli

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Biomarkers of traumatic brain injury – the biggest challenge of brain biomarker diagnostics?

Olli Tenovuo, Professor of Neurotraumatology at the University of Turku and the Head ofthe Turku Brain Injury Center at the Turku University Hospital. Finland

Traumatic brain injury (TBI) is a major public health concern, with an estimated 50 million new victims annually worldwide and costs possibly exceeding 500 billion € per year in Europe alone. TBI has been said as man's most complex disease in man's most complex organ. In this presentation I will point out the current major problems in TBI diagnostics, highlighting the vast need for reliable biomarker diagnostics. I will also go through the problems in developing biomarkers for clinical use in TBI, because of which the use is still negligible despite vast amount of research. Finally, I will give an overview on the current state of the field and the expected future views.

Selected publications:

- *The levels of GFAP and UCH-L1 during the first week after a traumatic brain injury:correlations with clinical and imaging findings. Neurosurgery 2016;79:456-64.*
- *Human serum metabolites associate with severity and patient outcomes in traumatic brain injury. EBioMedicine 2016;12:118-26.*
- *Serum metabolites associate with CT findings following TBI. Journal of Neurotrauma2018;35:2673-83.*
- *Early levels of GFAP and NF-L in predicting the outcome of mild TBI. Journal of Neurotrauma2019;36:1551-60.*
- *Blood biomarkers on admission in acute traumatic brain injury: Relations to severity, CTfindings and care path in the CENTER-TBI study. EBioMedicine 2020;56:102785.*

BRIDEL, Claire

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Fluid biomarkers in multiple sclerosis: hopes and reality

Claire Bridel, MD, PhD. Department of Clinical Neurosciences, Neurology Unit,Geneva University Hospital, Geneva, Switzerland.

Neurofilament light (NfL) is a biomarker of neuroaxonal injury, regardless of the underlying cause. Elevated levels of NfL in cerebrospinal fluid of individuals with a neurological condition were first reported 20 years ago. In multiple sclerosis (MS), NfLcorrelates with acute focal inflammation, and its levels often normalize in response to treatment. NfL has also been reported to predict disability and brain atrophy. In the past 5 years, interest in this biomarker has surged, mostly fueled by technical advances. Indeed, the development of ultrasensitive platforms now allows robust detection of NfL in blood, permitting less invasive and repetitive assessment of NfL. Potential clinical applications for NfL in MS are well-defined, yet NfL is still not available routinely to clinicians. After reviewing recent literature on NfL in MS, I will examine theremaining steps to be taken for clinical implementation, as a basis for discussion. Despite the potential of NfL as a biomarker in MS, there are still unmet needs. In particular, means to quantify disease progression are critically needed, as they may foster the development of specific treatments. Progression is a major contributor to long-term disability in MS, but treatments slowing this process are still lacking. More research into biomarkers is thus warranted, and interesting candidates are emerging,which I will review in the last part of the presentation.

QUADRIO, Isabelle

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Biomarkers for Neurodegenerative's diseases: where we stand, what's next ?

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Equipe BIORAN, Centre de recherche en Neurosciences de Lyon (CRNL).

Summary

Over 45 million people live with neurocognitive disorders worldwide and the number is estimated to increase to 130 million by 2050. Symptoms can be various and affect a wide range of cognitive functions. Evolution of these diseases is progressive, with long preclinical phases leading to a complete disability. On the molecular level, these diseases are characterized by progressive loss of neurons associated with deposition of aggregated proteins showing altered physicochemical properties. Detection of the accumulation of these proteins is now possible in preclinical / prodromal stages using cerebrospinal fluid biomarkers underlying pathophysiology of the diseases, especially for Alzheimer's disease. In the specific field of Prion's disease, originals and disease-specific assays based on seeded aggregation of the prion protein PrPsc has emerged in the past 10 years. This breakthrough technology has been adapted for various tissues and fluids and has recently been proposed in international diagnostic guidelines, even if its use in routine lab remains difficult due to safety consideration linked to Prion protein. For the other NCD to date, only surrogate biomarkers are proposed. Blood based biomarkers are under development and would probably been validated in the next future.

ELEVATOR PITCHES ABSTRACTS

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Blood biomarkers to detect atrial fibrillation as part of a primary stroke prevention strategy

Elena Palà, Alejandro Bustamante, Josep Lluis Clúa-Espuny, Juan Acosta, Felipe González, Juan Ballesta-Ors, Anna Penalba, Andrea Caballero, Jorge Pagola, Alonso Pedrote, Miguel Ángel Muñoz, Joan Montaner

Atrial fibrillation (AF) is a hearth rhythm disorder which increases the risk of ischemic stroke. Anticoagulation may reduce stroke risk in AF individuals but, due to its asymptomatic and paroxysmal nature, AF is usually undiagnosed and undertreated. In the present study, we performed a discovery and verification study to determine the usefulness of blood biomarkers as part of an AF screening strategy in a population with cardiovascular risk factors.

Subjects aged 65-75 years with hypertension and diabetes were included in the AFRICAT study, divided in two phases: Phase I (n=100) and Phase II (n=259). AF was assessed by conventional ECG and 4 weeks monitoring with a wearable Holter device (Nuubo^{TM}). Subjects with previous history of AF were excluded from Phase II. No AF cases with short (<100 hours) or bad quality registers were eliminated. A discovery experiment was performed using the proteomic platform SOMAscan in a group of 13 AF subjects vs 13 controls. The best candidates were selected and tested in whole cohort with immunoassaytechniques.

AF prevalence in our population was 9.7%. AF was detected in 18 individuals only after one-month Holter monitoring. In the discovery study, 40 proteins presented differential expression in AF. 18 proteins were evaluated in the whole Phase I using immunoassay techniques. From these, NT-proBNP, ST2 and TIMP2 were increased in AF and tested in thePhase II, but only NT-proBNP had increased levels in AF cases (p=0.154). In the whole cohort the combination of the three biomarkers had an AUC of 0.713 to detect AF and 0.610 to detect paroxysmal AF, a similar performance than NT-proBNP alone.

The results of the present study show the difficulty to find useful biomarkers to detect paroxysmal AF. According to our results NT-proBNP is the most promising candidate and there is a need to explore other biomarkers that could increase its performance.

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Blood biomarker panels for the early prediction of stroke-associated complications

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Background

Acute decompensated heart failure (ADHF) and respiratory tract infections (RTI) are potentially life-threatening complications in stroke patients during hospitalization. We aimed to test whether blood biomarker panels might predict these complications early after admission.

Methods and results

Nine hundred thirty-eight ischemic stroke patients were prospectively recruited in the Stroke- Chip study. Post-stroke complications during hospitalization were retrospectively evaluated. Blood samples were drawn within 6h after stroke onset and 14 biomarkers were analyzed by immunoassays. Biomarkers values were normalized using log-transformation and z-score. PanelomiX software was used to select panels with the best accuracy for predicting ADHF and RTI. Logistic regression models were constructed with the clinical variables and the biomarker panels. The additional predictive value of the panels compared to the clinical model alone was evaluated by ROC curves. An internal validation through 10-fold cross-validation with 3 repeats was performed. ADHF and RTI occurred in 19 (2%) and 86 (9.1%) cases, respectively. Three-biomarker panels were developed as predictors: VAP-1>5.67, NT-proBNP>4.98 and D- dimer>5.38 (sensitivity: 89.5%, specificity: 71.7%) for ADHF; and IL6>3.97, vWF>3.67 and D-dimer>4.58 (sensitivity: 82.6%, specificity: 59.8%) for RTI. Both panels independently predicted stroke complications (Panel for ADHF: OR (95% CI)=10.1(3-52.2), panel for RTI:

OR=3.73(1.95-7.14)) after adjustment by clinical confounders. The addition of the panel toclinical predictors significantly improved the AUCs of the ROC curves in both cases.

Conclusions

Blood biomarkers could be useful for the early prediction of ADHF and RTI. Future studies should assess the usefulness of these panels in front of stroke patients with respiratory symptoms such as dyspnea.

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Alpha-1 antitrypsin as a biomarker for stroke prognosis

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Patients' outcome prediction after stroke represents a crucial challenge. Alpha-1 antitrypsin (A1AT) is a serum proteinase inhibitor with anti-inflammatory and anti- apoptotic properties that increases in circulation within few hours after acute inflammatory responses. We aimed to explore the potential role of A1AT as diagnosis and prognosis stroke biomarker. To that end, blood from 80 ischemic (IS) and 25 hemorrhagic (ICH) stroke patients was drawn at hospital admission before treatment. Additionally, 8 control subjects free from brain lesions were included. Stroke patients were followed-up until 3rd month after the event and functional outcome was evaluatedaccording to the modified Rankin Scale (mRS; mRS<2 as good outcome and mRS≥2 as poor outcome).

No differences were found in A1AT levels among IS, ICH and controls. However, baselineA1AT levels were higher in those patients showing poor functional outcome at hospitaldischarge (p<0.001) and 3 months after the event (p<0.001). Cut-off values for each timepoint were selected using the Youden index, and the resulting dichotomized variables were added to a logistic regression model with the variables age, sex, baseline NIHSS and diabetes. A1AT baseline levels resulted to be an independent predictor of poor functional outcome at both studied time points (Adjusted odds ratio (ORadj): 7.41 [1.79-30.66], p=0.006 at discharge; ORadj: 4.64 [1.22-17.62], p=0.024 at 3rd month). Moreover, the addition of A1AT to the clinical model increased its discriminatory abilityby 6.44% at hospital discharge and 4.05% at 3rd month as measured by integrated discrimination improvement (IDI) index. Besides, we found that A1AT circulating levels were also associated with post-stroke respiratory infections (p=0.012). Overall, our datasuggest that A1AT could be used as a biomarker for stroke prognosis either in-hospital or at long term, as well as to discriminate those who would suffer from a respiratory infection after being hit by stroke.

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A panel comprising serum amyloid A, white blood cells and NIHSS for the triage of patients at low risk of post-stroke infection

Introduction. Accurate and early prediction of post stroke infections is important to improve antibiotic therapy guidance and/or to avoid unnecessary antibiotic treatment. We hypothesized that the combination of blood biomarkers with clinical parameters could help to optimize risk stratification during hospitalization.

Methods. The present study included 1379 patients (273 infected/1106 non-infected) from two independent European cohorts. In discovery (n=243) and validation cohorts (n=1136 patients) blood samples of ischemic stroke patients were collected at hospital admission within 72 hours from symptom onset. Prediction performances of blood biomarkers (Serum Amyloid-A (SAA), C-reactive protein (CRP), procalcitonin, white blood cells (WBC), creatinine) and clinical parameters(NIHSS, age, temperature) for the detection of post-stroke infection were evaluated individually using receiver operating characteristics curves. Panel combination performances were tested afterwards using an internal iterative threshold-based method called PanelomiX.

Results. At hospital admission the most specific markers for the stratification of patients at low risk of infection development were NIHSS, SAA and WBC, reaching sensitivity values of at least 90% and specificity of 31.3%, 26.4% and 25.4%, respectively. A panel combination of these three parameters significantly improved specificity values leading to 62.4% for more than 90% sensitivity.

Conclusion. At hospital admission a NIHSS, SAA and WBC combination appeared as a promising tool to improve the management of patients, avoiding unnecessary antibiotic treatmentin around half of them and consequently reducing resistance.

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Protein blood biomarkers in mild traumatic brain injury: CT triage at admission and outcome prediction

Background: More than 2.5 million of people are having traumatic brain injury each year in Europe. 90 % of those traumas are mild trauma (mTBI) and the clinical diagnosis of a potentiallesion is not always so obvious. CT-scans are performed to identify patients at risk of intracranial injuries; however, the majority will be CT-negative. Besides, 30% of patients keep post-concussion symptoms 6-months after their mTBI. Blood biomarkers have been studied for their use to predict CT-scan results. Here we investigate if AQP4 and A-FABP individuallyor in a panel with GFAP, S100b, H-FABP or IL-10 could perform better than the known mTBI biomarkers to both reduce number of unnecessary CT-scan and predict outcome.

Methods: Blood levels of the above proteins were measured using commercial immunoassays. Eighty-nine adult mTBI patients from Sevilla Hospital, having blood samples within six hours after their brain trauma and with at least one clinical symptom of mTBI were consequently selected. For the primary outcome, patients were dichotomized into CT-positiveor CT-negative groups. For the secondary outcome, we used the results of the Glasgow outcome scale to dichotomized patients into complete recovery (GOSE=8) and incomplete recovery (GOSE<8). Statistical analysis was performed using ROC curves and Panelomix onR software.

Results: Blood levels of HFABP, GFAP, IL-10 and S100b were significantly increased in CT-positive patients, and in patients with incomplete recovery at 6-months post-trauma. At 100%of sensitivity, the biomarker H-FABP had 55% and 58% of specificity to respectively predict CT-scans and outcome. Its performance to predict CT-scan was increased into panel with GFAP (SE: 100%, SP: 64%), IL-10 (SE: 100%, SP: 62%) or AQP4 (SE: 100%, SP: 60%).

Similar performances were observed for the outcome prediction, with IL-10 (SE: 100%, SP: 73%) or with AQP4 (SE: 100%, SP: 73%).

Conclusions: A biomarker panel consisting of HFABP and AQP4 yields the overall best performance of the studied biomarkers in separating patients with intracranial traumatic abnormalities from CT-negative patients and for the prediction of complete recovery at 6 month.

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Glioblastoma biomarkers: in vivo syngeneic and PDX mouse models to identify potentialbiomarkers

Sara G. Pelaz, Arantxa Tabernero

Background: Glioblastoma is the most aggressive and frequent primary brain tumor, typicallydetected when the tumor is of considerable size and complexity. Then, it is graded using invasive techniques (biopsy), and tumor size and recurrence are followed by neuroimaging using PET (radioactive tracers) and MRI scanning. Therefore, glioblastoma patients could greatly benefit from blood-borne biomarkers for prevention, diagnosis and monitoring of this type of cancer.

Methods and results: In our lab, we have set-up two mouse orthotopic glioblastoma models: a syngeneic model using Gl261 glioma stem cells, and a xenograft model using patient derived- glioblastoma stem cells (patient derived xenograft, PDX). We have used these animals to show an improved survival mediated by an anti-tumoral peptide we have developed (10.1093/neuonc/noz243); moreover, survival is also improved in these models when they are treated according to the human patient standard of care, the Stupp protocol (10.1016/j.canlet.2020.08.028). Finally, blood can be easily drawn from the animals prior to and during tumor development and treatment, as well as at end-point.

Conclusions: Hence, our proposal is to establish scientific collaborations to explore funding opportunities for the use of these models in the development of potential blood-borne biomarkers for: (1) early detection of glioblastoma and (2) monitoring of drug-based treatment outcomes (including drug resistance), through proteomic characterisation of circulating blood cells or plasma. Importantly, the clinical relevance and applicability of the identified potential biomarkers would be explored with data from public repositories and validated in samples from patient biobanks, such as the Spanish National DNA Bank.

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Accelerated Brain and Cardiac MR Image Reconstruction using DeepLearning

Ibtisam Aslam, Dr. Lindsey A CROWE, Dr. Miklos KASSAI, Prof. Jean-Paul VALLEE

Background: A major challenge in Magnetic Resonance Imaging (MRI) is long scan time and artifacts (off-resonance, geometric, susceptibility, chemical shift and motion)[1]. To accelerate MRI acquisition and reduce artifacts, a lesser amount of data should be acquired, but this leads to undersampling artifacts[2].

Methods: This work proposes a deep convolution neural network (2D Deep U-Net) to obtain an artifact free images from Compressed Sensing (CS)[3] under-sampled DWI Brain and multi-slice, single breath-hold highly accelerated radial cardiac cine images with better resolution for clinical diagnosis. Figure 1 shows the schematic diagram of proposed method.

The proposed 2D Deep U-Net has 10 & 14 convolution layers for Brain DWI & Cardiac data with a learning rate of 3×10^{-5}, 1×10^{-4} respectively; weight decay factor of 0.1; ReLu as an activation function and RMSPropoptimizer with an early stopping criterion of 400 epochs; these parameters are chosen after an extensive experimentation.

All calculation was done on Intel(R) Xeon(R) CPU,128GB RAM, and GPU NVIDIA GeForce GTX 1080Tei standalone system using TensorFlow as a backend[4] with python 3.8. The network training time was approximately 18 & 10 hours for Brain DWI and cardiac data, respectively. For brain DWI, the network was trained with 3 patients data tested on 10 patient's data. Similarly, for cardiac, 17 patient's data were used for training and 5 for testing. Image quality was assessed in terms of AP, RMSE, and SSIM values and analyzedusing student t-test with confidence interval (CI) of 95% at p-value < 0.05.

Results: Figure 2 & 3 show the reconstruction results of Brain DWI and Cardiac data. For brain DWI, 2D Deep U-Netgave 61% lesser AP, 54% lesser RMSE, and 31% higher SSIM than the conventional CS. Similarly, for the cardiac data, 31% lesser AP, 22% lesser RMSE and 4% improvement in SSIM than GROG U-Net.

Conclusion: Results confirm that the proposed 2D Deep U-Net network performs well for both brain and cardiac anatomyand provides improved quality images for clinical diagnostic.

Reference:

1. *D. Le Bihan, C. Poupon, A. Amadon, and F. Lethimonnier, "Artifacts and pitfalls in diffusion MRI," J.Magn. Reson. Imaging, vol. 24, no. 3, pp. 478–488, 2006.*
2. *Aslam, F. Najeeb, and H. Omer, "Accelerating MRI Using GROG Gridding Followed by ESPIRiTfor Non-Cartesian Trajectories," Appl. Magn. Reson., vol. 49, no. 1, pp. 107–124, Jan. 2018.*
3. *C. Zhang et al., "Acceleration of three-dimensional diffusion magnetic resonance imaging using a kernel low-rank compressed sensing method," Neuroimage, vol. 210, no. January, 2020.*
4. *C. M. Hyun, H. P. Kim, S. M. Lee, S. Lee, and J. K. Seo, "Deep learning for undersampled MRIreconstruction," Phys. Med. Biol., vol. 63, no. 13, p. aac71a, 2018*

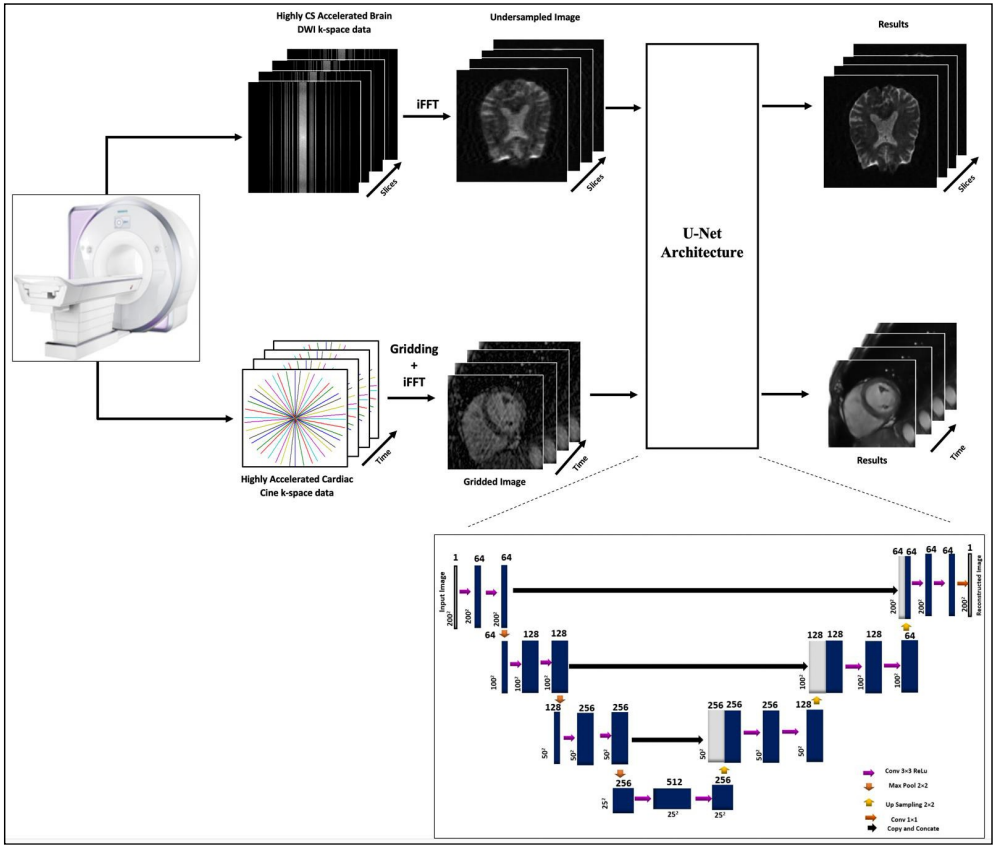

Figure 1: *A schematic illustration of the proposed method (2D Deep U-Net) for Brain DWI and Cardiac MR image reconstruction.*

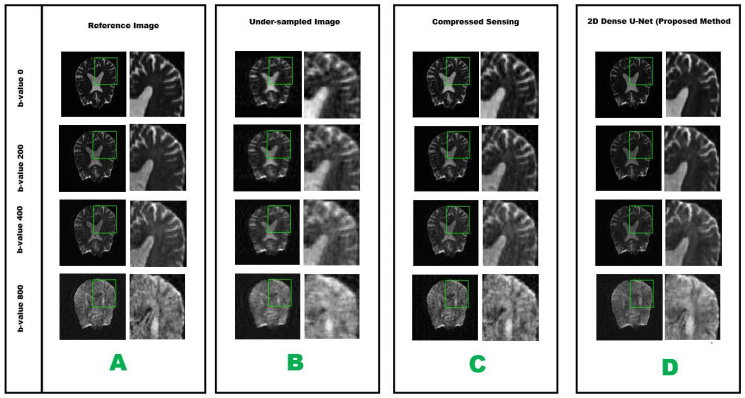

Figure-2: *Reconstruction results of the 3T human brain data (central slice) at AF=6 having different b-values i.e. 0,200,400 and 800 (s/mm²):* Column A: *Reference Image;* Column B: *Under-sampled Image;* Column C: *Compressed Sensing Reconstruction;* Column D: *Proposed Method Reconstruction (Column*

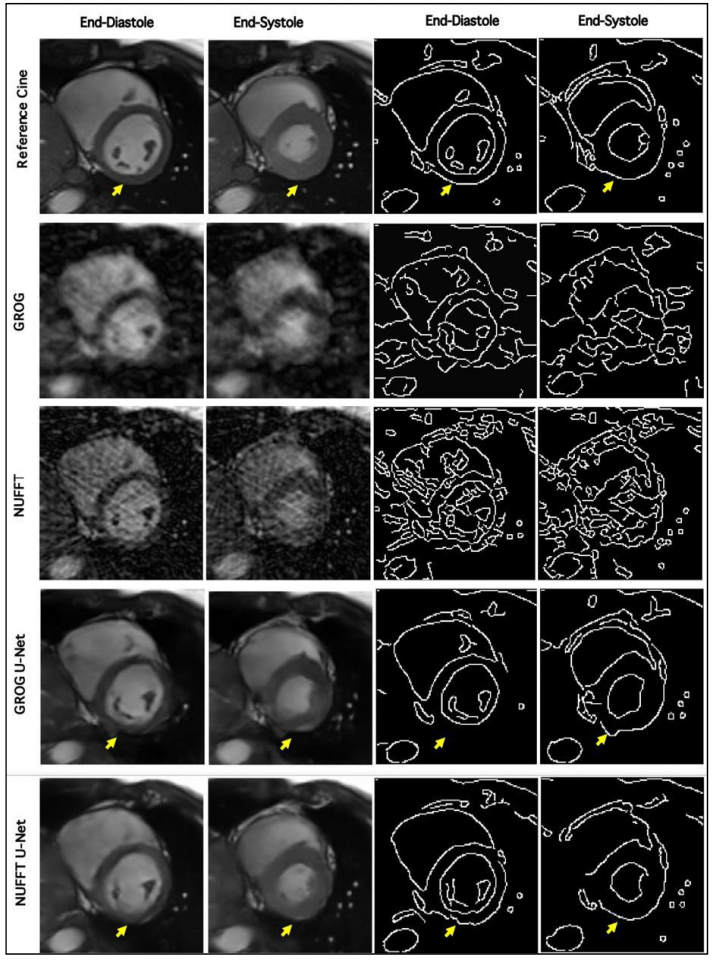

Figure 3*: Short axis End-diastole and End-Systole reconstructed images of a patient for whole heart cine Radial MR at acceleration factor 13 with 24 radial lines per image.* Reference cine*: Fully sampled image:* GROG*: undersampled GROG image* NUFFT: *undersampled NUFFT image.* GROG U-Net*: Reconstructed image of GROG using 2D Deep U-Net image,* NUFFT U-Net*: Reconstructed image of NUFFT using 2D Deep U-Netimage. Corresponding edges images provide visual image quality assessment Yellow arrows shows the myocardial wall distortion that is less pronounced in the NUFFT-U-Net.*

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Concordance between brain imaging and fluid biomarkers in Alzheimer's disease: evidence from the Geneva cohort

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**equally contributing*

Background. Alzheimer's disease is defined by the presence of amyloid and tau aggregates. The accumulation of such proteins can be assessed in vivo by dosing their levels in biological fluids (cerebrospinal fluid (CSF), and plasma), or by PET imaging. These biomarkers allow to classify subjectsaccordingly (A+/- and/or T+/-). Fluids and imaging biomarkers have however different strengths and weaknesses in terms of accessibility, costs and precision. As such, evidence on their concordance is ofcritical importance for clinical practice.

Methods. We analyzed all participants in ongoing clinical studies at the Nuclear Medicine and Molecular Imaging Division and Memory Center for which a combination of at least one of the following couple of measures was available: CSF and PET, CSF and plasma, plasma and PET. For CSF, we had concentration of Ab42, t-tau and p-tau181. Plasma p-tau181 levels were measured at the University of Gothenburg using an assay developed in-house on a Simoa HD-X instrument. CSF values were binarized using validated thresholds, while thresholds as in Shen et al, 2020 were used for plasma. PET images acquired using different tracers (Florbetapir and Flutemetamol for amyloid, Flortaucipir for tau) were binarized using standardized visual assessment.

Results. Amyloid PET and CSF Ab42 measures were concordant in 82% of the patients (N=166). Tau PET assessment was concordant with measures of CSF t-tau, CSF p-tau and plasma p-tau in 72% (N=36),67% (N=36) and 72% (N=69) of individuals, respectively.

Conclusions. Fluids and brain imaging biomarkers of A and T pathology were concordant in the majority of cases. A deeper understanding of the causes of discordance is a clinical priority.

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Next generation biomarkers for the early diagnosis of Alzheimer's disease

Introduction. Alzheimer's disease will affect 1 out of 6 people during lifespan while no efficient treatment is available yet. In addition, drug development is hampered by the lack of early diagnosis. Our consortia brings a solution by the identification of next-generation plasma biomarkers for the early detection of Alzheimer's disease.

Methods. Our double-blind retrospective study involves 400 patient sera sampled by the HUG. They were transferred to UniGe for processing funded by Innosuisse, then sent for mass spectrometry analysis at University of Seoul, South Korea, for biomarker discovery. Patent application is pending.

Results. Mass spectrometry analysis led to the identification of 154 candidate biomarkers showingdifferent expression pattern in healthy, mild cognitive-impaired and Alzheimer patients. Among these, the combination of 3 lead-biomarker showed sensitivity / specificity scores of >90%. Finally,our partner PCL Inc., South Korea, successfully measured these 3 leads directly in sera with their highly sensitive multiplex technology. This last step elicits a future use for routine diagnostics.

Conclusion. We identified a combination of 3 new Alzheimer biomarkers while we developed a fast and sensitive detection tool to elicit their use as a routine diagnosis. An additional prospectivestudy needs to be performed to provide additional information and strengthen our findings.

CREDITS

A certificate of attendance/participation may be delivered, so please contact us to obtain it. ECTS credits will be given based on the rule of your own doctoral school.

REGISRATION

Registration is free:

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