

EDITORIAL

doi: <https://doi.org/10.15407/ubj96.02.005>

RESEARCH CAPACITY BUILDING, NETWORKS, DEFINE RESEARCH STRATEGY, AND FUNDING OPPORTUNITIES IN RECOOP HST ASSOCIATION

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I built research capacity and networks for the first ten years in the RECOOP Research Consortium from 2002 to 2012. The RECOOP HST Consortium, with the financial support of Cedars–Sinai Medical Center (CSMC), applied for the International Visegrad Fund (IVF) grants. We applied for 20 Standard Grants and won 14 Standard Grants to support forming and managing research networks and multinational–multidisciplinary research projects. The IVF grants won by CSMC – RECOOP helped move toward the 21st Century and broaden the scope of activities in RECOOP. Also, the IVF grants helped to build support networks for biosafety and biosecurity, animal use in research, clinical research management, and research and Innovation management training. RECOOP HST Association implemented the Common Mechanism of Diseases (CMD) research program for innovative life science research in member countries. The objectives were to increase the number of young scientists participating in creative research. Knowledge sharing is the most essential element of collaborative research. Within the context of RECOOP, my final endeavor will focus on investigating the diagnosis and management of Post-Traumatic Stress Disorder (PTSD) in Ukraine. As of January 2024, an estimated 6.3 million people have been forced to flee Ukraine, with 94 percent of them hosted in European countries, representing 5.9 million refugees. In Ukraine, an estimated 7.8 million people need health assistance, and 11.5 million need protection assistance and services. Studies of PTSD report volume abnormalities in multiple regions of the cerebral cortex. However, findings for many regions, particularly regions outside commonly studied emotion-related prefrontal, insular, and limbic regions, are inconsistent and tentative. We, as researchers, must continually share our research findings and diligently replicate established methods and protocols. These tasks can often feel akin to the labor of Sisyphus. Moreover, within the scientific community, integrity is paramount; dishonesty is swiftly met with consequences akin to the justice administered by Zeus. Therefore, we researchers must roll a boulder up a hill again and again, and after we have proved that the published scientific work is sound, the “boulder” and the scientist will stay on top of the hill.

Key words: RECOOP HST Association, research capacity building and networks, define research strategy, funding opportunities, sciences and arts, Post Traumatic Stress Disorder (PTSD) in Ukraine, burden of Sisyphus.

RECOOP Legacy

Built research capacity and networks. I built research capacity and networks for the first 10 years in the RECOOP Research Consortium from 2002 to 2012. The RECOOP HST Consortium with the financial support of Cedars–Sinai Medical Center applied for the International Visegrad Fund Visegrad Fund grants. We applied 20 Standard Grants

and won 14 Standard Grants (20810243, 20820016, 20820040, 20820041, 20910138, 20920001, 20920002, 20920023, 20920024, 20910138, 21010083, 21010070, 21020052, and 21110096) to support the formation and management of research networks and multinational – multidisciplinary research projects [1]. The IVF grants won by CSMC – RECOOP helped move toward the 21st Century and

broaden the scope of activities in RECOOP. Also, the IVF Standard Grants helped to build support networks for Biosafety and Biosecurity, Animal use in Research, Clinical Research Management, and Research and Innovation Management Training [2]. The buildup of the RECOOP Life Science Research Platform sponsored by the International Visegrad Fund Strategic Grant (31110035) “Future of Visegrad Four Families Depends on Healthy Women and Children”. in the Visegrad Group to involves more young scientists in the new biotechnology developments, create innovative ideas, new medical treatment modalities in the region [3]. The results were reported during the Bridges in Life Sciences Conferences (Prague, Bratislava, Pecs, Bucharest, Zagreb, Budapest, and Lviv) and the Annual Scientific Review-Journal of the Biopolymers and Cell (www.biopolymers.org.ua)

Creative mind links Sciences and Arts. In 2024 the RECOOP HST Association will have the Ninth Sciences and Arts Competition <https://recoopsciart.net>. The main goal of the RECOOP Annual Art and Sciences Competition is to initiate creative working relations between sciences and arts, motivate scientists to create artworks from life science and medical images and communicate the beauty of the living organism. Sciences and Arts are sometimes described as separate human activities and mismatched. In my point of view art and science are not so disparate. They both require careful observation, intuition, inspiration, passion, dedication, and discipline and both can inspire each other [4]. In sciences and arts, creating something genuine based on the free association of ideas and views is essential. In sciences it has to be more guided toward a well-defined goal that is summarized in the hypothesis, in art it is a more spontaneous, logically unconstrained, and undirected association of ideas, emotions, and feelings.

Define Research Strategy. RECOOP HST Association implemented the Common Mechanism of Diseases (CMD) research program for innovative life science research in the Member Countries. The objectives were to increase the number of young scientists participating in innovative research, As part of the RECOOP Bridges Conference in 2015, the Association organized in Wroclaw we implemented the RECOOP Research Strategy: Common Mechanism of Diseases (CMD) and focused on Obesity has become epidemic [6]! The RECOOP scientists concluded that new approaches are required to

investigate the complex origin of obesity and related diseases, as obesity rates continue to rise in both the developed and the developing world. Scientists have come to recognize that body fat rather than body weight is the key to evaluating obesity. An excess of visceral fat is known as central obesity; the abdomen protrudes excessively as the “pot belly” or “beer belly”. This body type is also known as “apple-shaped” as opposed to “pear-shaped” in which fat is deposited on the hips and buttocks. Obesity is leading to diabetes, heart attack, stroke, kidney failure, blindness, and neurodegenerative diseases. Midlife obesity can lead to the development of AD, the silent killer of nerve cells. AD is also called “type 3 diabetes” because obese people with metabolic syndrome (also known as insulin resistance syndrome) are at higher risk for developing the disease. By 2025, the percentage of people in the EU population aged over 65 years is predicted to increase from 15.4% to 22.4%, which is likely to correlate with a rise in Alzheimer’s disease (AD), accounting for one-half to three-quarters of all dementia cases. Therefore, RECOOP started research grants to investigate the complex origin of obesity and related diseases [7].

Grant # 002: 2015-2017 Fruzsian Bagamery, Eva Szoko, Tamas Tabi, Budapest, Hungary. The role of insulin resistance and altered structure of lipid rafts in neurodegenerative disorders.

Grant # 007: 2017 Geza Muranszky, Livia Simon Sarkadi. Budapest, Hungary. Change in Fatty Acid Composition in Visceral–Subcutaneous Adipose tissue and Plasma of elderly pre-diabetic Rats.

Grant # 012: 2018-2020 Robert Gaspar, Szeged, Hungary. The role of obesity-induced low-grade inflammation in the adipokine signaling in pregnant rat uterus.

Grant # 016: 2019- 022 Reka Vass, Tibor Ertl, Pecs, Hungary. Pregnant Obesity and GDM change human milk secretory cytokines and alter IgG - IgA N-glycans and fatty acids.

Grant # 029: 2015-2022 Sandor G. Vari, Robert Gaspar, Eszter Ducza, Marija Heffer, Senka Blazetic, Vedrana Ivic, Tamas Tabi, Eva Szoko, Livia Simon-Sarkadi, Mate Szarka. RECOOP HST Association Obesity & Diabetes.

Increasing RECOOP’s funding opportunities. Knowledge sharing is the most important element of collaborative research. In cross-disciplinary collaborations, individual research work must be adapted to coordinate with other individual research works and researchers must discuss their results extensively

in workshops and at conferences. The production of new knowledge in medicine is facilitated by the enrichment of opportunities provided by efficient transnational multidisciplinary scientific partnerships and collaborations. These are the reasons why in 2006, Cedars–Sinai Medical Center (CSMC) with eleven Central and Eastern European (CEE) universities and academic organizations from 7 countries, Croatia, Czech Republic, Hungary, Romania, Slovakia, Poland, and Ukraine formed the Regional Cooperation for Health, Science, and Technology (RECOOP HST) Consortium [8]. In 2012, CSMC and the CEE partner organizations agreed to form the Association for Regional Cooperation in the Fields of Health, Science and Technology (RECOOP HST Association).

RECOOP is a strategic partnership that provides added value to both CSMC and the CEE organizations. The RECOOP HST Association enables the opportunity for the development of diverse talents in different specialties, all geared toward sharing and integrating knowledge. Therefore RECOOP implemented the Grants and Funds Mechanisms and Contract Modalities to support and foster research activities of the CSMC RECOOP Research Centers (CRRC) and projects that are strongly related to a RECOOP Common Mechanism of Diseases Research Strategy and areas of interest [9]. In this way created an environment that facilitates the efficient and effective utilization of the RECOOP funds.

Scientific ideas, uphill battle. Scientific work for researchers is an endless challenge. Determining new markers for early diagnosis of diseases, investigating the maintenance of cell and tissue homeostasis, and studying metabolic regulation and dysregulation as well as intra-organ, interorgan regulatory, and metabolic crosstalk can be tiresome work and can sometimes seem like the punishment Zeus gave to Sisyphus [10]. The Greek mythological figure was also infamous for his deception though, which had led Zeus to punish him. Sisyphus was condemned to roll a boulder up a mountain but near the top of the mountain, the boulder rolled down, for eternity Sisyphus was forced to repeat this task over and over. While scientific research can sometimes seem like this, the cleverness of scientists helps to overcome the “Sisyphus Effect”. Albert Camus essay he wrote, “*Zeus leaves Sisyphus at the foot of the mountain. One always finds one’s burden again. But Sisyphus teaches the higher fidelity that negates the gods and raises rocks*”. Sisyphus is a symbol of

self-overcoming and moving toward ever more sophisticated, expressive, beautiful, and potent modes of action and expression. In the RECOOP HST Association, scientists equally share the burden of Zeus and Sisyphus independently of gender status [11]. I know from Albert Camus’ essay that Sisyphus is Happy. “*Each atom of that stone, each mineral flake of that night-filled mountain, in itself, forms a world. The struggle itself toward the heights is enough to fill a man’s heart. One must imagine Sisyphus happy*”. I am a Sisyphus, and I am happy.

We researchers have to share our research results as well as repeat the published methods and research protocols again and again and these tasks can seem like “Sisyphean” work. Furthermore, in Science, the research community also plays the role of Zeus and will punish dishonesty so therefore we researchers must roll a boulder up a hill again and again and after we have proved that the published scientific work is sound, the “boulder” and the scientist will stay on top of the hill [12].

My last effort was to make something good. Support the diagnosis and management of Post Traumatic Stress Disorder (PTSD) in Ukraine. In RECOOP as my last effort, I will work on researching the diagnosis and management of Post Traumatic Stress Disorder (PTSD) in Ukraine. As of January 2024, an estimated 6.3 million people have been forced to flee Ukraine, with 94 percent of them hosted in European countries representing 5.9 million refugees. In Ukraine, an estimated 7.8 million people need health assistance, and 11.5 million need protection assistance and services. The ongoing return of internally displaced persons is exacerbating needs. The recent surge in strikes and Russian hostilities caused extensive damage across Ukraine, including at least 10 healthcare facilities. It affected essential services where hundreds of thousands were left without electricity and water amid harsh weather conditions. In Ukraine, an estimated 2.5 million need mental health services. The ongoing return of internally displaced persons is exacerbating needs. Ukraine Emergency Situation Report #22 (17 January 2024) - Ukraine | ReliefWeb. RECOOP HST Association is working on a project to define the principal medical needs of soldiers, veterans, and civilians in the Ternopil, Lviv, and Kyiv regions. RECOOP researchers already used the International Trauma Questionnaire (ITQ) an 18-question self-report measure focusing on the core features of Post Traumatic Stress Disorder (PTSD) and Complex

PTSD (CPTSD). It was developed to be consistent with the organizing principles of the ICD-11. <https://novopsych.com.au/assessments/diagnosis/international-trauma-questionnaire-itq/>

RECOOP partners are planning to establish a regional model for research, training, and education programs to manage and treat PTSD. Our effort combines artificial intelligence, and computerized databases for soldiers fighting with the Russians and with rats in the trenches. We would like to involve the Ministry of Digital Transformation in using machine learning for data analysis and artificial intelligence for health and social data integration to support the diagnosis and management of PTSD [13].

This list integrates biomarkers that have been directly linked to PTSD, as well as those with potential relevance due to their roles in neuroinflammation, neurodegeneration, and brain-environment interactions [14-17].

CSF Flow Markers: Beta-trace protein (BTP), Albumin.

CSF Markers Also Detectable in Serum: S100B (Calcium-binding protein B).

Neurodegenerative Disease Markers: Tau protein, Beta-amyloid (A β 40, A β 42), Neurofilament light (NfL), Glial fibrillar acidic protein (GFAP).

Extracellular Matrix (ECM) Proteins; Fibronectin, Laminin.

Inflammatory Markers; Cytokines (IL-6, TNF- α , IL-1 β), Pro-inflammatory cytokines (IL-2, IL-17), IL-6 (Interleukin-6), TNF- α (Tumor Necrosis Factor- α), MCP-1 (Monocyte Chemoattractant Protein-1), CX3CL1 (Fractalkine).

Oxidative Stress Markers; Malondialdehyde (MDA); Superoxide Dismutase (SOD), Glutathione (GSH).

Growth Factors and Receptors; Platelet-derived growth factor receptor beta (PDGFR β).

Neurotrophins and Growth Factors; BDNF (Brain-Derived Neurotrophic Factor).

Hormones and the HPA Axis; Cortisol, DHEA (Dehydroepiandrosterone), and DHEA-S.

Matrix Metalloproteinases; MMP-2; MMP-9.

Aquaporins: Aquaporin-4 (AQP4).

We have begun compiling a list of different studies for each biomarker [18, 19].

Neuroimaging. Studies of posttraumatic stress disorder (PTSD) report volume abnormalities in multiple regions of the cerebral cortex. However, findings for many regions, particularly regions outside commonly studied emotion-related prefrontal,

insular, and limbic regions, are inconsistent and tentative. These findings indicate that cortical volumes in PTSD patients are smaller in prefrontal regulatory regions, as well as in broader emotion and sensory processing cortical regions. The prefrontal cortex (the front-most part of your neocortex) helps you think through decisions, observe how you're thinking, and put on the "brakes" when you realize something you first feared isn't a threat after all. Your prefrontal cortex helps regulate emotional responses triggered by the amygdala. In service members with PTSD, the prefrontal cortex doesn't always manage to do its job when needed. An overactive amygdala combined with an underactive prefrontal cortex creates a perfect storm. This might help to understand why someone with PTSD might: 1 - feel anxious around anything even slightly related to the original trauma that led to the PTSD; 2 - have strong physical reactions to situations that shouldn't provoke a fear reaction, and 3 - avoid situations that might trigger those intense emotions and reactions [20].

Cerebrospinal fluid (CSF) plays an essential role in maintaining the homeostasis of the central nervous system. PTSD is changing the functions of CSF including [1] buoyancy of the brain, spinal cord, and nerves; [2] volume adjustment in the cranial cavity; [3] nutrient transport; [4] protein or peptide transport; [5] brain volume regulation through osmoregulation; (6) buffering effect against external forces; [7] signal transduction; [8] drug transport; [9] immune system control; [10] elimination of metabolites and unnecessary substances; and finally cooling of heat generated by neural activity [21]. Over the past 40 years, scientific methods of "neuroimaging" have enabled scientists to see that PTSD causes distinct biological changes in the left and right temporal lobes in your brain. Not everybody with PTSD has the same symptoms or the same brain changes, but there are observable patterns that can be understood and treated [22].

White matter alterations indicate PTSD symptom severity, as well as patterns of reduced volume in the prefrontal cortex. These results contribute to the developing profile of neuroanatomical differences uniquely attributable to veterans who suffer from chronic PTSD [23].

Gray matter (GM) reduction was identified in the medial prefrontal cortex in PTSD. Additional GM reduction was also observed in PTSD in the left hippocampus, left middle temporal gyrus, and right superior frontal gyrus [24, 25].

The amygdala triggers your natural alarm system. Your amygdala is a primitive, animalistic part of your brain that's wired to ensure survival. PTSD will change your alarm system. When it's overactive, it's hard to think rationally. When somebody experiences a disturbing event, it sends a signal that causes a fear response. Exposure to trauma can activate the amygdala which is responsible for fear responses. It results in hypervigilance and inappropriate fear responses. Those with PTSD tend to have an overactive response, so something as harmless as a car backfiring could instantly trigger panic. The good news is that also shows evidence that successful treatment of PTSD with therapies such as EMDR Eye movement desensitization and reprocessing (EMDR) and Cognitive behavioral therapy (CBT) do produce measurable structural changes in brain regions associated with fear conditioning. Alternating focus between past traumas and present thoughts could disrupt the efficacy of both therapies. For example, EMDR aims to process memories while CBT encourages detachment from those memories [26].

Your hippocampus is a lot like your computer's memory that writes files to its hard drive. After a trauma, your hippocampus works to remember the event accurately and make sense of it. PTSD experiences such as unwanted feelings that pop up out of nowhere or always being on the lookout for threats that could lead to more trauma seem to be related to the hippocampus, or the memory center of your brain. But because trauma is typically overwhelming, all the information doesn't get coded correctly. This means that you might have trouble remembering important details of the event, or you might find yourself thinking a lot about what happened because your hippocampus is working so hard to try to make sense of things. Numerous studies have explored the relationship between posttraumatic stress disorder (PTSD) and the hippocampus and the amygdala because both regions are implicated in the disorder's pathogenesis and pathophysiology [27].

РОЗВИТОК ДОСЛІДНИЦЬКОГО ПОТЕНЦІАЛУ, СТВОРЕННЯ МЕРЕЖ, ВИЗНАЧЕННЯ СТРАТЕГІЇ ДОСЛІДЖЕННЯ ТА МОЖЛИВОСТІ ФІНАНСУВАННЯ В АСОЦІАЦІЇ RECOOP HST

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Я нарощував дослідницький потенціал і створював мережі протягом перших десяти років у консорціумі RECOOP HST з 2002 року по 2012 рік. Консорціум RECOOP HST за фінансової підтримки медичного центру Cedars-Sinai (CSMC) подав заявку на гранти Міжнародного вишеградського фонду (IVF). Із 20 заявок на стандартні гранти виграли 14 стандартних грантів на підтримку формування та управління дослідницькими мережами і міжнаціональними багатодисциплінарними дослідницькими проєктами. Гранти IVF, виграні CSMC – RECOOP, допомогли рухатись у 21-е століття та розширити сферу діяльності RECOOP. Крім того, гранти IVF допомогли побудувати мережі підтримки для біобезпеки та біозахисту, використання тварин у дослідженнях, управління клінічними дослідженнями та навчання менеджменту досліджень та інновацій. Асоціація RECOOP HST реалізувала дослідницьку програму Загального механізму захворювань (CMD) для інноваційних досліджень у галузі науки про життя в країнах-членах RECOOP. Завдання полягали в тому, щоб збільшити кількість молодих учених, які беруть участь у творчих дослідженнях. Обмін знаннями є найважливішим елементом спільного дослідження. У контексті RECOOP моя остання спроба буде зосереджена на дослідженні

діагностики та лікування посттравматичного стресового розладу (ПТСР) в Україні. Станом на січень 2024 року приблизно 6,3 мільйона людей були змушені покинути Україну, 94% з них розміщені в європейських країнах, тобто 5,9 мільйонів біженців. В Україні, за оцінками, 7,8 мільйонів людей потребують медичної допомоги, а 11,5 мільйонів потребують допомоги та послуг із захисту. Дослідження ПТСР повідомляють про аномалії об'єму в багатьох областях кори головного мозку. Однак результати пов'язані з емоціями префронтальної, островної та лімбічної областей мозку, є суперечливими та умовними. Дослідники, повинні постійно ділитися результатами своїх досліджень і старанно відтворювати встановлені методи та протоколи. Ці завдання часто нагадують тяжку працю Сізіфа. Крім того, у науковому співтоваристві чесність має першорядне значення; нечесність швидко стикається з наслідками, подібними до правосуддя Зевса. Тому ми, дослідники, повинні знову і знову котити валун на пагорб, і після того, як ми доведемо, що опублікована наукова робота обґрунтована, «валун» і вчений залишаться на вершині пагорба.

Ключові слова: Асоціація RECOOP HST, розвиток дослідницького потенціалу та мережі, визначення стратегії дослідження, можливості фінансування, наука та мистецтво, посттравматичний стресовий розлад (ПТСР) в Україні, тягар Сізіфа.

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