



Volume
145

in **ADVANCES**
MEDICINE *and*
BIOLOGY

Leon V. Berhardt
Editor

Complimentary Contributor Copy

ADVANCES IN MEDICINE AND BIOLOGY

**ADVANCES IN MEDICINE
AND BIOLOGY**

VOLUME 145

LEON V. BERHARDT
EDITOR



Complimentary Contributor Copy

Copyright © 2019 by Nova Science Publishers, Inc.

All rights reserved. No part of this book may be reproduced, stored in a retrieval system or transmitted in any form or by any means: electronic, electrostatic, magnetic, tape, mechanical photocopying, recording or otherwise without the written permission of the Publisher.

We have partnered with Copyright Clearance Center to make it easy for you to obtain permissions to reuse content from this publication. Simply navigate to this publication's page on Nova's website and locate the "Get Permission" button below the title description. This button is linked directly to the title's permission page on copyright.com. Alternatively, you can visit copyright.com and search by title, ISBN, or ISSN.

For further questions about using the service on copyright.com, please contact:

Copyright Clearance Center

Phone: +1-(978) 750-8400

Fax: +1-(978) 750-4470

E-mail: info@copyright.com.

NOTICE TO THE READER

The Publisher has taken reasonable care in the preparation of this book, but makes no expressed or implied warranty of any kind and assumes no responsibility for any errors or omissions. No liability is assumed for incidental or consequential damages in connection with or arising out of information contained in this book. The Publisher shall not be liable for any special, consequential, or exemplary damages resulting, in whole or in part, from the readers' use of, or reliance upon, this material. Any parts of this book based on government reports are so indicated and copyright is claimed for those parts to the extent applicable to compilations of such works.

Independent verification should be sought for any data, advice or recommendations contained in this book. In addition, no responsibility is assumed by the Publisher for any injury and/or damage to persons or property arising from any methods, products, instructions, ideas or otherwise contained in this publication.

This publication is designed to provide accurate and authoritative information with regard to the subject matter covered herein. It is sold with the clear understanding that the Publisher is not engaged in rendering legal or any other professional services. If legal or any other expert assistance is required, the services of a competent person should be sought. FROM A DECLARATION OF PARTICIPANTS JOINTLY ADOPTED BY A COMMITTEE OF THE AMERICAN BAR ASSOCIATION AND A COMMITTEE OF PUBLISHERS.

Additional color graphics may be available in the e-book version of this book.

Library of Congress Cataloging-in-Publication Data

ISBN: ; 9: /3/75837/; 47/9*gdqqm-

ISSN: 2157-5398

Published by Nova Science Publishers, Inc. † New York

Complimentary Contributor Copy

CONTENTS

Preface		vii
Chapter 1	Milestones in the Reproductive Process: Involvement of the Oviduct Environment <i>Estefanía Massa and Sergio Ghersevich</i>	1
Chapter 2	Role of Tenofovir in Occupational HIV Post-Exposure Prophylaxis <i>Amanda L. Palcic and Olga M. Klibanov</i>	69
Chapter 3	Vacuole of Eukaryotic Cells: A Sophisticated Niche for Intracellular Bacteria <i>Farideh Siavoshi and Samira Heydari</i>	87
Chapter 4	Histone Deacetylase 3 and Its Inhibitors <i>Sk. Abdul Amin, Nilanjan Adhikari, Balaram Ghosh and Tarun Jha</i>	131
Chapter 5	Anti Inflammatory Mechanisms and Effect of Celecoxib for Endoneural Stem Cells Survival in Spontaneous Intracerebral Hemorrhage <i>Robert Sinurat</i>	203

Chapter 6	Deposition of Foreign Proteins in Plant Vacuoles: A Unique Characteristic of Plant-Based Platforms <i>Silvana Petruccelli</i>	215
Contents of Earlier Volumes		263
Index		269

Chapter 5

**ANTI INFLAMMATORY MECHANISMS
AND EFFECT OF CELECOXIB
FOR ENDONEURAL STEM CELLS
SURVIVAL IN SPONTANEUS
INTRACEREBRAL HEMORRHAGE**

Robert Sinurat*

Surgery Department, Universitas Kristen Indonesia,
Jakarta, Indonesia

ABSTRACT

Spontaneous intracerebral hemorrhage (SICH) is part of a hemorrhage stroke type with high morbidity and mortality. Neuron cells die in SICH due to primary injury caused by compression and damage directly by blood clots, and secondary injury by the neuroinflammation process. When the neuroinflammation process was very excessive, normal or dying neuron cells can die too. Besides the dying cells process, there was also migration of

* Cooresponding Author's Email: robertsinurat@yahoo.com.

endoneural stem cells from their niches in the hippocampus and subventricle zones to the lesion area which was triggered by differentiation quantity of stromal derived factor-1 (SDF-1) between niches and the lesion area. Only small amounts of these neural stem cells can be differentiated to adult neuron cells, while the others could not survive due to the impact of neuroinflammation. Celecoxib as selective cox 2 inhibitor can decrease the neuroinflammation itself by preventing the production of prostaglandin E2 (PGE2) from arachidonic acid, and decreased fas ligand (FasL) expression which is important for activation of caspase 8 and 3 as extrinsic pathway apoptosis. In this article, the author showed algorithm of cell dead mechanism in SICH and how the impact of intraperitoneal celecoxib treatment can increase the survival of neural stem cells.

Keywords: neuroinflammation, apoptosis, cox, survival

INTRODUCTION

Stroke is a neurologic disease resulting from brain vessels occlusion (ischemic stroke) or ruptures (hemorrhage stroke). Hemorrhage stroke is divided into intracerebral and subarachnoid hemorrhage. Intracerebral hemorrhagic is due to ruptures of small penetrating arteries, secondary to hypertensive changes or other vascular abnormalities. The highest risk factor was hypertension. Spontaneous intracerebral hemorrhage (SICH) incidence was not changed in the last 30 years and was the highest in Asia. The incidence rate per 100, 000 person-years was 51,8 in Asia, 24,2 in whites, 22,9 in blacks, and 19,6 in Hispanic [1, 2].

SICH fatality rates were 25 - 30% in developed countries and 30-48% in the non developed countries [3]. In one month, a case fatality rate of SICH is approximately 40%, and increased about 54% at 1 year. Only 12% to 39% of patients can have long-term functional independence [2].

Every effort must be carried out to decrease those fatality rates and increasing outcomes of SICH patients. The author reviewed pathophysiology of SICH and proposes a new algorithm of cell dead mechanism in SICH and the impact of intraperitoneal celecoxib treatment to increase the populations of neural stem cells in the lesion zone.

DIAGNOSIS AND UPDATE MANAGEMENT OF SICH

All patients with severe headache suddenly, vomiting and decreased level of consciousness progressively must be first managed as SICH patients. After stroke attacks, patients can get worse for a few hours with a decrease of Glasgow Coma Scale (GCS) because of hypoxia or haematoma expansion. To prevent hypoxia, stabilisation of the airway with breathing and circulation (ABCs) management is essential for preventing secondary brain injury. Endotracheal tube insertion is crucial for airway protection of patients with GCS 8 or lower, and another patient with significant respiratory distress. When ABCs management is completed, a computerized tomomography (CT) scan is performed to show intracerebral haematoma location and extension, volume, mass effect and hydrocephalus [4, 5]. A peripheral blood test was needed to rule out deficiency of coagulation factors and should accept replacement treatment immediately [6]. Indications of surgery for hematoma evacuation were dependent on haematoma volume, location and mass effect of haematoma. American Heart and Stroke Association had guidelines up to date in 2015 for the management of SICH including surgery indications and management of hypertension. The guidelines recommended that patients with systolic blood pressure (SBP) between 150mm Hg and 200mmHg were safely decreased to 140mm Hg. It was effective for improving functional outcome [6, 7]. The blood pressure of patients with SBP >220mm Hg should be reduced with continuous antihypertensive drug intravenous infusion and frequent monitoring. Any clinical deterioration in association with aggressive reduction of blood pressure should be reviewed for the blood pressure target. Nicardipine titration is one of the intravenous calcium channel blocker's choice for blood pressure reduction, and oral antihypertensive agents can be initiated as soon as possible. Angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB), calcium channel blocker (CCB) and a thiazide-like diuretic at maximal are recommended for resistant hypertension [6, 8].

Craniotomy for clot removal was indicated for fossa posterior haematoma with > 3cm in diameter, especially when brain stem compression

or hydrocephalus exists. Procedures were approved for supratentorial haematoma while any evidence of deterioration due to haematoma volume or edema expansion, and minimal invasive surgery plus recombinant tissue-type plasminogen activator for ICH evacuation trial II (MISTIE II) suggested a better outcome. The MISTIE III trial is on progress [6, 9]. Severe intraventricular extensions of hemorrhage with or without hydrocephalus needed placement of external ventricular drainage [4, 10]. Mannitol 0,5 – 1 gram intra vein bolus was indicated for elevated intracranial pressure with mass effect and herniation [4].

PROGNOSTICS FACTORS

Many factors are involved in the outcome of SICH. Some poor prognostic factors were low grade of GCS, haematoma volume $> 30\text{Cm}^3$, hemorrhage intraventricular extension, and old age > 80 years old [11]. Fever and high vital signs also increased mortality and morbidity in SICH patients [12, 13].

NEUROINFLAMMATION AND NEURON CELL DEATH

When brain vessels were ruptured, the hematoma compressed the neurons and glia immediately, and micro vascular ischemic was involved. Then glutamate was released. Calcium influx into cells and mitochondria failed. Sodium was accumulated and cell became edema and necrotic. It was primary injury mechanisms for spontaneous intracerebral haematoma. The primary injury is always followed by secondary injury as a neuroinflammation response to blood products as hemoglobin, thrombin, ferrous, haemin, ferrous, and halotransferin. Microglia was activated by those to produce reactive oxygen species (ROS), matrix metalloproteinase (MMP), Cyclooxygenase 2 (Cox2), Prostaglandin (PG), heme oxygenase-1 (HO-1),

complement factor, tumor necrotizing factor- α (TNF α), and interleukin 1 β (IL-1 β) [7, 14].

ROS, TNF α , and IL-1 β will increase Aquaporin 4 (AQ4) expression and blood brain barrier (BBB) damage. BBB permeability was increased. Vasogenic edema showed up, and macrophage recruitment like polymorphonuclear (PMN), especially neutrophil, was engaged to destruct the brain [7, 14, 15]. Meanwhile, caspase enzyme will be activated by complement C3a, C5a, TNF- α , and Interleukin 1 β to induce apoptosis process of neuron and glia [7, 16]. Heme as eritrosit derivative from hematoma was degraded into bilirubin and bilirubin oxidation products (BOXes).

They also activate microglia and astrocytes to release cytokine which contributes to neuron and glial detrimental effects [17].

Cyclooxygenase (Cox) enzyme was involved in neuroinflammation, especially cox-2. Cyclooxygenase 1 (Cox-1) and cyclooxygenase 2 (Cox-2) can changes arachidonic acid and become prostaglandin PGG2 and PGH2 before they have changed into one of these five prostanoids. The prostanoids were prostacycline (PGI2), thromboxan (TxA2), prostaglandin D2 (PGD2), prostaglandin F2 (PGF2), or prostaglandin E2. Prostaglandin E2 became involved in the initiation and propagation of neuroinflammation. PGE-2 was produced by prostaglandin E synthases (PGES).

There were 3 types of PGES that change PGH2 into PGE2, microsomal PGES-1 (mPGES-1), microsomal PGES-2 (mPGES-2) and cytosolic PGES (cPGES). Cytosolic PGES were involved in Cox1 pathway, and mPGES-1 in Cox-2 pathway, while microsomal mPGES-2 related to golgi membrane were released into plasma. Four types of PGE2 receptors consisting of EP1, EP2, EP3, dan EP4. EP1 activation increased intra cell calcium 2+ level, while EP3 decreased cyclic adenosine monophosphate (cAMP) [18, 19]. Cox-2 will induce Fas Ligand (FasL) expression, which is important for activation of caspase 8 and 3 as an extrinsic pathway apoptosis [20]. Cox-2 also overactivates N methyl D- aspartate (NMDA) receptors causing excessive influx of Ca²⁺ and leads to excitotoxicity [21].

**CELECOXIB AS COX-2 INHIBITOR
FOR NEUROPROTECTION**

Celecoxib is a selective cox-2 non steroidal anti-inflammatory drug (NSAID). Many authors reported impact of celecoxib for protection of neuron and glia. Combination of celecoxib and memantine were reported to decrease hematoma volume, brain edema and induce neurology recovery [22]. Celecoxib can inhibit cox2 and become a neuroprotector by decreasing synthesis of prostanoids, free radicals and protected neuron from excitotoxicity from NMDA receptors in ischemic stroke [21, 23]. One researched treatment by injected celecoxib and sodium chloride intraperitoneally to intracerebral rats model resulted in a decreasing of brain edema and perihematoma cell death [24]. Efficacy of administration of celecoxib 400mg twice a day can reduce the perihematoma edema in the acute stage of SICH patients [25].

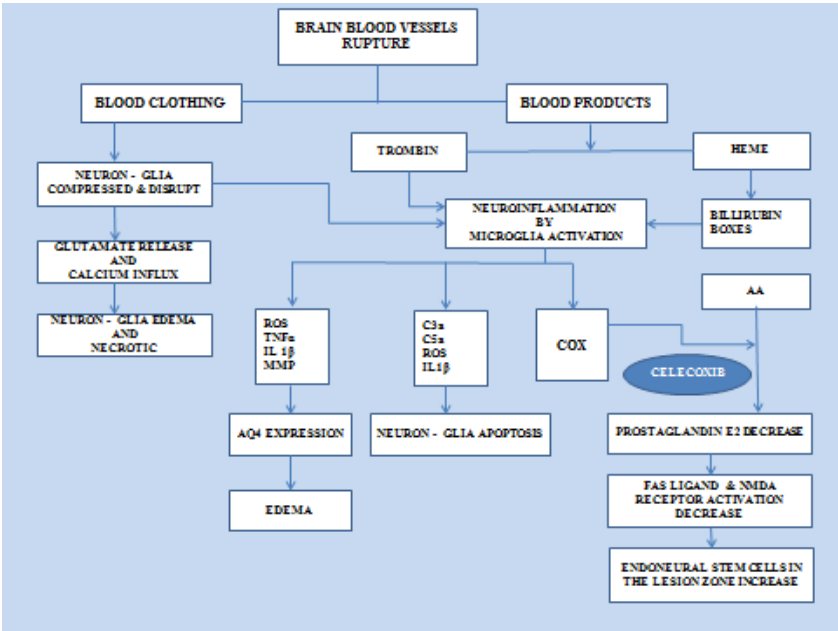


Figure 1. Cell death mechanisms of SICH, and cox inhibition by celecoxib to increase neural stem cells in the lesion zone.

Besides neuroinflammation processes, endoneural stem cells were migrated from the niche (hippocampus and subventricles zone) into the lesion zone around the haematoma as neurogenesis [26]. But most of them (80%) died because of inflammation [27]. The author had treated SICH rat models with celecoxib injection intraperitoneally 20mg/kg body weight. The results conclude that the population of endoneural stem cells in the lesion zone was higher compared to controls. When celecoxib reduced the cox-2 activation, FasL expression and NMDA receptor activation were reduced. Thus excessive neuroinflammation was inhibited, and more neural stem cells can survive [28].

NEW ALGORITHM OF SPONTANEOUS INTRACEREBRAL HAEMATOMA

With all of the previous knowledge and many author's and researcher's results, the author proposes an algorithm of the cell death mechanism in SICH and impact of intraperitoneal celecoxib treatment to increase the survival of neural stem cells in the lesion zone (Figure 1).

REFERENCES

- [1] Poon, Michael T. C., Simon M. Bell and Rustam A. Shalman, 2015. "Epidemiology of Intracerebral Haemorrhage". *Frontiers of Neurology and Neuroscience*, 37:1 - 12. Accessed November 2015. doi:10.1159/00437109.
- [2] Van Asch, Charlotte J. J., Merel J. A. Luitse, Gabriel J. E. Rinkel, Ingeborg van der Tweel, Ale Algra and Catharina J. M. Clijin, 2010. "Incidence, Case Fatality, and Functional Outcome of Intracerebral Hemorrhage Overtime, According to Age, Sex, and Ethnic Origin: A Systematic Review and Meta-Analysis". *The Lancet Neurology*, 9:167 - 76. Accessed January 6, 2010. doi:10.1016/S1474-4442(09)70340-0.

- [3] Feigin, Valery L., Carlene M. M. Lewis, Derrick A. Bennet and Suzanne L. Barker-Collo, 2009. "Worldwide Stroke Incidence and Early Case Fatality Rate Reported in 56 Population-Based Studies: A Systematic Review". *The Lancet Neurology*, 8:355 - 69. Accessed February 21, 2009. doi:10.1016/S1474-4442(09)70025-0.
- [4] Dastur, Cyrus K. and Wengui Yu, 2017. "Current Management of Spontaneous Intracerebral Hemorrhage". *Stroke and Vascular Neurology*, 2(1):21 - 9. Accessed February 24, 2017. doi:10.1136/svn-2016-000047.
- [5] Rincon, Fred and Stephan A. Mayer, 2008. "Clinical Review: Critical Care Management of Spontaneous Intracerebral Hemorrhage". *Critical Care*, 12(6):237. Accessed December 10, 2008. doi:10.1186/cc7092.
- [6] Hemphill III, Jesse C., Steven M. Greenberg, Craig S. Anderson, Kyra Becker, Bernard R. Bendok, Mary Cushman, Gordon L. Fung, Joshua N. Goldstein, R. Loch Macdonald, Pamela H. Mitchell, Phillip A. Scott, Magdy H. Selim and Daniel Woo, 2015. "Guidelines for the Management of Spontaneous Intracerebral Hemorrhage". *Stroke*, 46:2032 - 60. Accessed May 25, 2015. doi:10.1161/STR.0000000000000069.
- [7] Qureshi, Adnan I., A. David Mendelow and Daniel F. Hanley, 2009. "Intracerebral Haemorrhage". *Lancet*, 373(975):1632 - 44.
- [8] Calhoun, David A., Daniel Jones, Stephen Textor, David C. Goff, Timothy P. Murphy, Robert D. Toto, Anthony White, William C. Cushman, William White, Domenic Sica and Keith Ferdinand, 2008. "Resistant Hypertension: Diagnosis, Evaluation, and Treatment". *Hypertension*, 51:1403 - 19. Accessed April 7, 2008. doi:10.1161/Hypertensionaha.108.189141.
- [9] Mould, W. Andrew, J. Ricardo Carhuapoma, John Muschelli, Karen Lane, Timothy C. Morgan, Nichol A. McBee, Amanda J. Bistran-Hall, Natalie L. Ullman, Paul Vespa, Neil A. Martin, Issam Awad, Mario Zuccarello and Daniel F. Hanley, 2013. "Minimally Invasive Surgery plus rt-PA for Intracerebral Hemorrhage Evacuation (MISTIE)

- Decreases Perihematomal Edema”. *Stroke*, 44(3):627 - 34. Accessed February 7, 2013. doi:10.1161/STROKEAHA.111.000411.
- [10] Veltkamp Roland and Jan Purucker, 2017. “Management of Spontaneous Intracerebral Hemorrhage”. *Current Neurology and Neuroscience reports*, 17:80. Accessed September 8, 2017. doi:10.1007/s11910-017-0783-5.
- [11] An, Sang J., Tae J. Kim and Byung W. Yoon, 2017. “Epidemiology, Risk Factors, and Clinical Features of Intracerebral Hemorrhages: An Update”. *Journal of Stroke*, 19 (1):3 - 10. Accessed January 31, 2017. doi:10.5853/jos.2016.00864.
- [12] Greer, David M., Susan E. Funk, Nancy L. Reaven, Myrsini Ouzounelli and Gwen C. Uman, 2008. “Impact of Fever on Outcom in Patients With Stroke and Neurologic Injury, A Comprehensive Meta-Analysis”. *Stroke*, 39:3029-35. Accessed August 21, 2008. doi:10.1161/STROKEAHA.108.521583.
- [13] Hasan, Zaki N., Kareem M. Al Tameemi and Gazhi F. Alhaji, 2012. “Predictors of Outcome for Spontaneous Intracerebral Hemorrhage in Iraqi Stroke Patients”. *Internal Medicine: Open Acces*, 2:111. Accessed June 29, 2012. doi:10.4172/2165-8048.1000111.
- [14] Wang Jian and Sylvain Dore, 2007. “Heme Oxygenase-1 Exacerbates Early Brain Injury after Intracerebral Hemorrhage”. *Brain*, 130 (Pt6):1643-52. Accessed June 01, 2007. Doi:10.1093/brain/ awm095.
- [15] Wang, Jian. 2010. “Preclinical and Clinical Research on Inflammation after Intracerebral Hemorrhage”. *Progress in Neurobiology*, 92(4):463 - 77. Accessed August 14, 2010. doi:10.1016/j.pneurobio.2010.08.001.
- [16] Yang, Shuxu, Takehiro Nakamura, Ya Hua, Richard F. Keep, John G. Younger, Yangdong He, Julian T. Hoff and Guohua Xi, 2006. “The Role of Complement C3 in Intracerebral Hemorrhage-Induced Brain Injury”. *Journal of cerebral Blood Flow and Metabolism*, 26(12):1490 - 5. Accessed December 1, 2006. doi:10.1038/ sj.jcbm.9600305.
- [17] Loftspring, Matthew C., Craig Hansen and Joseph F. Clark, 2010. “A Novel Brain Injury Mechanism after Intracerebral Hemorrhage: the Interaction between Heme Products and the Immune System”.

- Medical Hypotheses*, 74(1):63 - 6. Accessed August 28, 2009. Doi:10.1016/j.mehy.2009.08.002.
- [18] Yang, Hongwei and Chu Chen, 2008. "Cyclooxygenase-2 in Synaptic Signaling". *Current Pharmaceutical Design*, 14(14):1443 - 51.
- [19] Zhao, Bing-Q., Emiri Tejima and Eng H. Lo, 2007. "Neurovascular Proteases in Brain Injury, Hemorrhage and Remodelling after Stroke". *Stroke*, 38:748 - 52. Accessed February 1, 2007. doi:10.1161/01/STROKE.00000253500.32979.d1.
- [20] Callaghan, Grace O., Jaqueline Kelly, Fergus Shanahan and Ailen Houston, 2008. "Prostaglandin E2 Stimulates Fas Ligand Expression via the EP1 Receptor in Colon Cancer Cell". *British Journal of Cancer*, 99(3):502 - 12. Accessed July 22, 2008. doi:10.1038/sj.bjc.6604490.
- [21] Hewett, Sandra J., Tracy F. Uliasz, Aniruddha S. Vidwans and James A. Hewett, 2000. "Cyclooxygenase-2 Contributes to N-Methyl-D-Aspartate-Mediated Neuronal Cell Death in Primary Cortical Cell Culture". *Journal of Pharmacology and Experimental Therapeutics*, 293(2):417 - 25.
- [22] Sinn, Dong I., Soon T. Lee, Kon Chu, Keun H. Jung, Eun C. Song, Jeong M. Kim, Dong K. Park, Manho Kim and Jae K. Roh, 2007. "Combined Neuroprotective Effects of Celecoxib and Memantine in Experimental Intracerebral Hemorrhage". *Neuroscience Letters*, 411(3):238 - 42.
- [23] Mc Cullough, Louise, Liejun Wu, Norman Haughey, Xibin Liang, Tracey Hand, Qian Wang, Richard M. Breyer and Katrin Andreasson, 2004. "Neuroprotective Function of the PGE₂ E2 Receptor in Cerebral Ischemia". *Journal of Neuroscience*, 24(1):257-68. Accessed January 7, 2004. doi:10.1523/JNEUROSCI.4485-03.2004.
- [24] Chu, Kon, Sang W. Jeong and Keun H. Jung. 2004. "Celecoxib Induces Functional Recovery after Intracerebral Hemorrhage with Reduction of Brain Edema and Perihematoma Cell Death". *Journal of Cerebral Blood Flow and Metabolism*, 24(8):926 - 33. Accessed August 1, 2004. doi:10.1097/01.WCB.0000130866.25040.7D.

- [25] Lee, Seung H., H. K. Park, Wi Sun Ryu, Jae S. Lee, Hee J. Bae, M. K. Han, Y. S. Lee, Hyung M. Kwon, Chi K. Kim, E. S. Park, Jong W. Chung, Keun H. Jung and Jae K. Roh. 2013. “ Effects of Celecoxib on Hematoma and Edema Volumes in Primary Intracerebral Hemorrhage: A multicenter randomized controlled trial”. *The Official Journal of the European Academy of Neurology*, 20(8):1161-9. Accessed March 29, 2013.doi:10.1111/ene.12140.
- [26] Shen, Jianfeng, Lin Xie, Xiaou O. Mao, Yongqing Zhou, Renya Zhan, David A. Greenberg and Kunlin Jin. 2008. “ Neurogenesis after Primary Intracerebral Hemorrhage in Adult Human Brain”. *Journal of Cerebral Blood Flow and Metabolism*, 28(8):1460 - 8. Accessed April 30, 2008.doi:10.1038/jcbfm.2008.37.
- [27] Ekdahl, Christine T., Jan H. Claasen, Sara Bonde, Zaal Kokaia and Olle Lindvall. 2003. Inflammation is Detrimental for Neurogenesis in Asult Brain. *Proceedings of the National Academy of Sciences of the United States of America*, 100(23): 13632 - 37. Accessed October 27, 2003. doi: 10.1073/pnas.2234031100.
- [28] Sinurat, Robert, Ani M. Maskoen, Dany Hilmanto and Kahdar Wiriadisastra. 2016. “Role of SDF-1 and Celecoxib in Increasing Quantity of Neural Stem Cell in the Lesion Zone and Outcome of Spontaneous Intracerebral Hemorrhage”. *International Journal of Pharmacy and Pharmaceutical Sciences*, 8(7):399 - 403.

BIOGRAPHICAL SKETCH

Robert Sinurat

Affiliation: Surgery Department Universitas Kristen Indonesia, Jakarta, Indonesia.

Education: Neurosurgeon, PhD

Business Address: Jalan Mayjen Sutoyo, Cawang, Jakarta Timur, Indonesia, 13650.

Research and Professional Experience: PhD program

Publications from the Last 3 Years:

- [1] 2016, *International Journal of Pharmacy and Pharmaceutical Sciences*, 8(7):399 - 403.
- [2] 2017, Incidental Bleeding Meningioma, *Asian Journal of Neurosurgery*, 12(2):247 - 49.