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**PEMERINTAH PROVINSI JAWA TIMUR**  
**RUMAH SAKIT UMUM DAERAH Dr. SOETOMO**  
Jl. Mayjen. Prof. Dr. Moestopo 6-8, Telp. 031-5501071-5501073, Fax. 5501164.  
**SURABAYA - 60286**



**KEPUTUSAN**  
**DIREKTUR RUMAH SAKIT UMUM DAERAH DOKTER SOETOMO**  
**NOMOR : 188.4/ 99.1 /301/2017**

**TENTANG**  
**PENETAPAN PENELITIAN UNGGULAN TERPILIH YANG DIBIAYAI**  
**RUMAH SAKIT UMUM DAERAH Dr. SOETOMO SURABAYA**

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**DIREKTUR RUMAH SAKIT UMUM DAERAH DOKTER SOETOMO**

- Menimbang : a. Bahwa RSUD Dr. Soetomo sebagai Rumah Sakit Pendidikan kelas A yang berbasis riset mempunyai kewajiban menjamin keterselenggaranya penelitian unggulan untuk menunjang peningkatan mutu pelayanan dan pendidikan kesehatan seiring dengan kemajuan teknologi kesehatan dan kedokteran terkini.
- b. Bahwa agar penelitian unggulan berbasis kebutuhan dan mencerminkan dinamika keilmuan klinik dan manajemen perumaksuditan yang mendukung orientasi *best practice* dan *problem solving*, maka perlu didukung pembiayaan oleh RSUD Dr. Soetomo.
- c. Bahwa agar pelaksanaan penelitian unggulan terpilih untuk pembiayaannya sebagaimana butir a dan b dapat terlaksana dengan optimal dan efektif perlu ditetapkan dengan Keputusan Direktur RSUD Dr. Soetomo.
- Mengingat : 1. Undang-undang RI. Nomor: 18 Tahun 2002 tentang Sistem Nasional Penelitian, Pengembangan dan Penerapan Ilmu Pengetahuan dan Teknologi;
2. Undang-Undang RI. Nomor: 25 Tahun 2009 tentang Pelayanan Publik (Lembaran Negara Republik Indonesia Tahun 2009, Nomor: 112, Tambahan Lembaran Negara Republik Indonesia Nomor: 5038);
3. Undang-Undang RI. Nomor: 36 Tahun 2009 tentang Kesehatan (Lembaran Negara Republik Indonesia Tahun 2009, Nomor: 144, Tambahan Lembaran Negara Republik Indonesia Nomor: 5063);
4. Undang-Undang RI. Nomor: 44 Tahun 2009 tentang Rumah Sakit (Lembaran Negara Republik Indonesia Tahun 2009, Nomor: 153, Tambahan Lembaran Negara Republik Indonesia Nomor: 5072);
5. Peraturan Pemerintah Nomor: 39 Tahun 1995 tanggal 14 Nopember 1995, tentang Penelitian dan Pengembangan Kesehatan;



6. Keputusan Menteri Kesehatan RI. Nomor: 1179 A/MENKES/SK/X/1999 tanggal 11 Oktober 1999, tentang Kebijakan Nasional Penelitian dan Pengembangan Kesehatan;
7. Peraturan Daerah Provinsi Jawa Timur Nomor: 11 Tahun 2008 tanggal 20 Agustus 2008 tentang Struktur Organisasi dan Tata Kerja Rumah Sakit Daerah Provinsi Jawa Timur (Lembaran Daerah Provinsi Jawa Timur Tahun 2008 Nomor: 4 Seri D);
8. Peraturan Gubernur Jawa Timur Nomor: 112 Tahun 2008, tanggal 22 Agustus 2008 tentang Uraian Tugas Direktur, Wakil Direktur, Bidang, Bagian, Seksi dan Sub Bagian di Rumah Sakit Umum Daerah Provinsi Jawa Timur;
9. Keputusan Gubernur Jawa Timur Nomor: 188/438/KPTS/013/2008, tanggal 30 Desember 2008 tentang Penetapan RSUD Dr. Soetomo Sebagai Badan Layanan Umum Daerah

#### MEMUTUSKAN

Menetapkan :

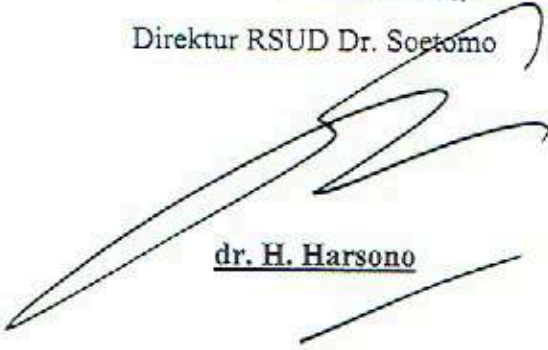
- Pertama : Menetapkan Keputusan Direktur RSUD Dr. Soetomo tentang Penetapan Peneliti Penelitian Unggulan yang terpilih untuk dibiayai oleh Rumah Sakit Umum Daerah Dr. Soetomo Surabaya;
- Kedua : Menetapkan peneliti unggulan baik *Clinical Trial* maupun *Health Service Research (HSR)* berdasarkan ketentuan yang sudah ditetapkan oleh tim reviewer Penelitian Unggulan;
- Ketiga : Pemilihan dan penentuan terhadap peneliti yang terpilih dilaksanakan melalui mekanisme seleksi yang cermat berdasarkan:
1. Judul yang diajukan orisinal, relevan dengan kebijakan Penelitian Unggulan sebagaimana kebijakan pimpinan RSUD Dr. Soetomo baik yang *Clinical Trial* maupun *Health Service Research (HSR)* berdasarkan keilmuan maupun secara etis.
  2. Kebenaran dokumen yang diajukan oleh peneliti.
  3. Daftar kebutuhan penelitian harus berdasarkan ketentuan anggaran yang diberikan oleh rumah sakit.
- Keempat : Bahwa biaya yang diberikan untuk *Clinical Trial* sebesar Rp. 50.000.000,- (Lima Juta Rupiah) termasuk pajak, untuk *Health Service Research (HSR)* sebesar Rp. 15.000.000,- (Lima Belas Juta Rupiah) termasuk pajak;
- Kelima : Daftar nama peneliti yang terpilih dari RSUD Dr. Soetomo sebagaimana tercantum dalam lampiran Keputusan ini;
- Keenam : Semua biaya Penelitian Unggulan RSUD Dr. Soetomo Tahun 2017 dibebankan pada DPA-BLUD dengan Tahun Anggaran 2017;

- Ketujuh : Keputusan ini berlaku sejak tanggal ditetapkan dan apabila di kemudian hari ternyata terdapat kekurangan dan kekeliruan akan diadakan perubahan dan perbaikan sebagaimana mestinya;
- Kedelapan : Salinan Keputusan ini disampaikan kepada yang bersangkutan untuk diketahui dan dilaksanakan dengan sebaik-baiknya.

Ditetapkan di : S U R A B A Y A

Pada tanggal : 04 JAN 2017

Direktur RSUD Dr. Soetomo



dr. H. Harsono



Lampiran 1

Lampiran : Keputusan Direktur RSUD Dr. Soetomo

Nomor : 188.4/99-1/301/2017

Tanggal : 04 JAN 2017

**NAMA PENELITI *CLINICAL TRIAL* YANG TERPILIH  
RUMAH SAKIT UMUM DAERAH Dr. SOETOMO SURABAYA  
TAHUN 2017**

JUDUL PENELITIAN	KEDUDUKAN DALAM TIM	NAMA
1	2	3
Analisis Perubahan Suhu Kulit Perifer dan Panjang Keliling Pembuluh Darah Vena Perifer Bagian Distal Pasca Regional Blok Anestesi Terkait Keberhasilan Blok	Peneliti Utama	1. Dr. Christijogo Sumartono.dr.,SpAn.,KAR
	Anggota	1. Soni Sunarso Sulistiawan.dr.,SpAn 2. Belindo Wirabuana.dr.,SpAn 3. Herdiani Sulisty Putri.dr.,SpAn 4. Arif Johansyah.dr.
Profil IgE serum, IL-4, IL-10, IL-17, interferon gamma, limfosit CD4+ dan indeks skoring atopik dermatitis (SCORAD) pada pasien dermatitis atopik dewasa yang diterapi dengan lactobacillus plantarum dan placebo	Peneliti Utama	2. dr. Trisniartami, SpKK
	Anggota	1. Abdul Karim,dr 2. Laissa Bonita,dr 3. Dr. Cita Rosita S.P.,
Faktor Risiko Infeksi Dengue Berat Pada Anak	Peneliti Utama	3. Dr. Dominicus Husada.dr., DTM&H., MCTM(TP).SpAn (K)
	Anggota	1. Senja Baiduri,dr.
Efikasi Fisioterapi Standar ditambah Latihan Berjalan diatas Treadmill Dibandingkan Fisioterapi Standar Terhadap Fungsi Motorik Kasar Anak Palsi Serebral Tipe Spastik Diplegia	Peneliti Utama	4. Prastiya Indra Gunawan,dr.,SpA
	Anggota	1. Prof. Darto Saharso,dr., SpA(K) 2. Dr. Ratna Darjanti Haryadi,dr.,SpKFR(K) 3. Dr. Arief Wibowo,dr.,MS 4. dr. Lusiana
Perbandingan Ekspresi Peroxiredoxin-2 (PRDX2), IL-6, P53, Dan VEGF pada Proliferasi Pterigium Primer dan Rekuren	Peneliti Utama	5. Dr. Hendrian Dwikoloso Soebagjo,dr., Sp.M.(K)
	Anggota	1. Eddyanto,dr.,SpM(K) 2. Danang Saksono,dr 3. Shinta Arta Wiguna,dr 4. A. Nur Ummah,dr 5. Wibawanindya Wahyuresti,dr
Pengaruh Prakondisi Hipoksia terhadap Ekspresi Reactive Oxygen Spesies (ROS) pada Kultur Human Adipose Derived Mesenchymal Stem Cells (H-ASC)	Peneliti Utama	6. dr.IG Rurus Suryawan,Sp.JP(K) FIHA
	Anggota	1. Andrianto,dr.,SP.JP FIHA 2. dr. Ratna Dewi C
Perbandingan Efikasi Kemoterapi Regimen Vinorelbin-Karboplatin Dengan Vinorelbin-Sisplatin Pada Adenokarsinoma Paru EGFR Mutasi Negatif Stadium Lanjut	Peneliti Utama	7. Dr.Laksmi Wulandari.,Sp.P(K),FCCP
	Anggota	1. dr. Anna Febriani.,Sp.P 2. dr. Fara Fatmawati.,Sp.P 3. dr. Wirya Sastra Amran



Hubungan Antara Paparan Bising Dengan Kadar Reactive Oxygen Species (ROS) dan Gangguan Fungsi Pendengaran Pada Karyawan RSUD Dr. Soetomo yang Berisiko Tinggi	Peneliti Utama	8. Dr. Nyilo Purnami,dr.,SpT.H.T.K.L(K), FICS,FISCM
	Anggota	1. dr. Serafika Permoni Putri Manyakori
Efek Latihan Isometrik dan Neuromuscular Electrical Stimulation Intradialis Terhadap IL-15, IL-16, dan TNF- $\alpha$ dan Kapasitas Fungsi Pasien Penyakit Ginjal Kronik	Peneliti Utama	9. Dr. Hening Laswati,dr.,Sp.KFR(K)
	Anggota	1. Dewi Poerwandari,dr.,SpKFR 2. Widodo,dr.,Sp.PD-KGH(K) 3. Maysita Damayanti,dr
Pemberian Sildenafil Sitrat Menurunkan hs-CRP dan Meningkatkan Internasional Index of Erectile Function-5 Pada Penderita Disfungsi Ereksi Sedang	Peneliti Utama	10. Judie Hartono, dr., MS,Sp.And
	Anggota	1. Tjahjo Djojo Tanojo,dr.,MS.,Sp.And 2. IGN Pramesemara, dr.,M.Biomed 3. Rossy Sintya Marthasari, dr.,M.Biomed 4. Ahmad Ricardo Syukur,dr. 5. Rezia Oktarina,dr,
Asosiasi Rasio Th 17/ T-reg dengan Derajat Keparahan Penyakit Systemic Lupus Erythematosus	Peneliti Utama	11. Dr. Yuliasih,dr.,Sp.PD, K-R
	Anggota	1. dr. Rizki Maulidya Putri, dr 2. Tri Yanti , dr 3. Adidia Carina Familia,dr
Pengaruh Stem Cell Darah Menstruasi Terhadap Folikel Ovarium Pada Tikus Yang Mendapat Cisplatin	Peneliti Utama	12. Dr. Hendy Hendarto,dr.,SpOG (K)
	Anggota	1. dr. Birama Robby Indraprasta
Perbandingan Efektifitas Terapi Rat Bone Marrow Stem Cell Secara Intraperitoneal dan Intravena pada Tikus Model Sindroma Ovarium Polistik Terhadap Folikulogenesis dan Ekspresi TGF- $\beta$	Peneliti Utama	13. Prof.Dr.H. Budi Santoso,dr.,SpOG (K)
	Anggota	1. dr. Hardian Optario Sinaga
Pengaruh Diet Ketogenik Terhadap Glasgow Prognostic score,TNF- $\alpha$ dan Laktat Serum sebagai Indikator Inflamasi Sistemik dan Metabolik Pada Pasien Kanker Kolorektal dengan "Best Supportive Care"	Peneliti Utama	14. Dr. Vicky S Budipramana,dr.,SpB-KBD
	Anggota	1. dr. Fransiscus Arifin,SpB 2. dr. Rudy Napitupulu,SpB
Faktor Risiko Terjadinya Mukositis Oral Pada Anak Dengan Leukimia Limfoblastik akut di RSUD Dr. Soetomo	Peneliti Utama	15. Nining Dwi Suti Ismawati,drg.,SpBM
	Anggota	1. Achmad Harijadi,drg.,SpBM 2. Dr. Roedi Irawan,dr.,M.Kes,Sp.A(K) 3. Ellen Satya Pratiwi, drg.
Komorbiditas Gangguan Jiwa Pada Pasien dengan Penyakit Medik dan Bedah di RSUD Dr. Soetomo Surabaya	Peneliti Utama	16. Agustina Konginan,dr., Sp.KJ (K)
	Anggota	1. Suksmi Yitnamurti,dr., SpKJ(K) 2. Azimatul Karimah,dr.,SpKJ(K) .FISCM 3. DR. Margarita M Maramis,dr.,SpKJ(K). FISCM 4. Nalini Muhdi,dr., SpKJ(K) 5. Khairina,dr.,SpKJ(K)



Korelasi Antara Rentang Waktu Operasi dengan Jumlah Sel satelit yang Mengekspresikan MyoD Pada Otot Biceps Penderita Cedera Pleksus Brakhialis	Peneliti Utama	17. Dr. Heri Suroto, dr.,Sp.OT (K)
	Anggota	1. Gestana R. Wardhana,dr.
Pengaruh Demineralized Bone Matrix Terhadap Diferensiasi Osteogenik Pada Adipose Stem Cell dan Bone Marrow Stem Cell : Sebuah uji In Vitro	Peneliti Utama	18. Dr. Ferdiansyah, dr.,Sp.OT(K)
	Anggota	1. Christopher Antony Simandjuntak,dr.
Perbandingan Jumlah Osteoblast dan Alkaline Phosphatase pada Small Bone Defect Os Femur New Zealand white Rabbit Yang Diberi Cuttlefish dan Bovine Bone Xenograft	Peneliti Utama	19. Dr. Komang Agung I.S,dr.,SpOT(K)
	Anggota	1. Ameria Pribadi,dr.
Pengaruh Decellularized Cartilage Bovine Scaffold dan Kondisi Hypoxia Terhadap Diferensiasi Stem Cell Menjadi Kondrosit Secara In Vitro	Peneliti Utama	20. dr. Tri Wahyu Martanto,Sp.OT(K)
	Anggota	1. Dr. Dwikora N. Utomo,dr.,Sp.OT(K) 2. Dr. Ferdiansyah Mahyudin,dr.,Sp.OT(K) 3. Aries Rakhmat Hidayat,dr
Pengaruh Teknik Deselularisasi Terhadap Kadar Kolagen Tipe II dan Porositas Matriks Cartilage Bovine Scaffold	Peneliti Utama	21. Dr. Dwikora Novembri U, dr.,Sp.OT(K)
	Anggota	1. Ferdiansyah Mahyudin,dr.,Sp.OT(K) 2. Tri Wahyu Martanto,dr.,Sp.OT(K) 3. Ika Benny Kartikasari,dr.
Penggunaan fetal free-DNA dalam Darah Ibu Hamil sebagai Teknik uninvative pada paternity test (test keayahan)	Peneliti Utama	22. Dr. Ahmad Yudianto, dr.SpF, SH.,M.Kes
	Anggota	1. Prof.Dr.Med.HM.Soekry Erfan Kusuma,dr.,SpF(K), DFM
Pola Bakteri Penyebab Infeksi dan Kepekaan Antibiotik Pasien Rujukan PPK 2 Guna Penyusunan Terapi Empirik	Peneliti Utama	23. Hari Paraton, dr.,SpOG(K)
	Anggota	1. Prof.Dr.Kuntaman, dr.,MS,SpMK(K) 2. Vera Yuanita,dr
Akurasi dan Efisiensi Metode Sel Blok Untuk Pelayanan Diagnostik Kanker Paru Melalui Prosedur Biopsi Aspirasi Jarum Halus Dengan Tuntunan CT Scan	Peneliti Utama	24. Etty Hari Kusumastuti,dr., Sp.PA(K)
	Anggota	1. Nila Kurniasari,dr.,SpPA 2. Heriyawati,dr.,SpPA

Direktur RSUD Dr. Soetomo

dr. H. Harsono



Lampiran 2

Lampiran : Keputusan Direktur RSUD Dr. Soetomo

Nomor : 188.4/99.1/301/2017

Tanggal : 04 JAN 2017

**NAMA PENELITI HEALTH SERVICE RESEARCH (HSR) YANG TERPILIH  
RUMAH SAKIT UMUM DAERAH Dr. SOETOMO SURABAYA  
TAHUN 2017**

JUDUL PENELITIAN	KEDUDUKAN DALAM TIM	NAMA
1	2	3
Evaluasi Penerapan clinical Pathway (CP) Tuberkulosis (TB) paru di ruang Palem RSUD Dr. Soetomo Surabaya	Peneliti Utama	1. Tutik Kusmiati,dr.,SpP(K)
	Anggota	1. Alfian Nur Rosyid,dr.,Sp.P(K)
Analisis Faktor Risiko Timbulnya Hospital Acquired Pneumonia (HAP)	Peneliti Utama	2. Umi Fatmawati,S.Farm., M.Pharm.Klin,Apt
	Anggota	1. Dra. Endang Martiani, M.Pharm.,Apt 2. Dewi Makmuroh Nurul Qomar Purnamawati, S.Farm,Apt
Analisis Kelengkapan Data Diagnosis Dalam Rekam Medik Nomor 12 Terkait Outcome Dan Simulasi Pembiayaan BPJS Pada Pasien di RSUD Dr. Soetomo Surabaya	Peneliti Utama	3. Anna Surgean Veterini,dr., SpAn.,KIC
	Anggota	1. Kun Arifi Abbas,dr.,SpAn 2. Wahyu Mananda,dr.,SpAn 3. Teuku Aswin Husain,dr.,SpAn 4. Soni Sunarso Sulistiawan,dr., SpAn.FIPM 5. Ahmad Amin Mahmudin,dr. 6. Dede Subrata,dr
Stabilitas Penyimpanan Sampel untuk Pemeriksaan Darah Lengkap	Peneliti Utama	4. dr. Yetti Hernaningsih,dr.,SP.PK
	Anggota	1. Arie Rahmanitarini,dr.
Pengaruh Pemakaian BRACA Dalam Meningkatkan Citra Diri Pada Pasien dengan Kanker Payudara Paska Mastektomy di RSUD Dr. Soetomo Surabaya	Peneliti Utama	5. Iskandar Ali,dr., Sp.B(K).Onk
	Anggota	1. Dewi Maryam, S.Kep.Ns,M.Kep 2. Sri Endang P.,S.Kep.Ns.M.Kes
HubunganAntara Kepatuhan Petugas Kesehatan Untuk Mencuci Tangan dengan Kejadian Infeksi Nosokomial di Ruang Rosella 1 dan Rosella 2 RSUD Dr. Soetomo Surabaya	Peneliti Utama	6. Hafifah Parwaningtyas,S.Kep.Ns
	Anggota	1. Aris Setiyono,Amd.Kep 2. Chilmia Aris Tsania,S.Kep.Ns 3. Ucik Nurul Hidayanti,Amd.Kep
Pengaruh Asessmen Awal Keperawatan Dengan Konsep Formula ATOE terhadap Peningkatan Prosentase Waiting Time di Instalasi Rawat Jalan RSUD Dr. Soetomo Surabaya	Peneliti Utama	7. Erfandi Ekaputra, S. Kep.Ns
	Anggota	1. Ari Suwandari, M. Kep 2. Nur Rofiati, S. Kep. Ns 3. Dwi Yuni Astutik, S. Kep. Ns 4. Wiwik Andayani, S.Kep.Ns



Analisis Biaya Pasien Infeksi Rumah Sakit (Health Associated Infection) di RSUD Dr. Soetomo	Peneliti Utama	8. Mariyatul Qibtiyah, S.Si, Apt, SpFRS
	Anggota	1. Prof. Dr. Kuntaman, dr., MS., SpMK (K) 2. Bambang Pujo Semedi, dr., SpAn.KIC 3. Prof. Dr. Usman Hadi, dr., PD-KPTI 4. Pepy Dwi Endraswari, dr., M.Si 5. Ika Nindya Kadariswantiningsih, dr., M.Sc. 6. Neneng Dwi Kurniati, dr., Sp.MK
Efektivitas Sterilisasi dengan Sinar Ultraviolet dan Desinfeksi Dalam Penurunan Jumlah Angka Kuman Di Ruang Operasi RSUD Dr. Soetomo	Peneliti Utama	9. Horima, ST
	Anggota	1. Suhariono, ST., MT 2. Alis Indah Suciati, Amd.KL 3. Intan Permata, Amd.KL 4. Abdul Chodir, S.KM., M.KL
Analisis Perbandingan Total Biaya Pemeriksaan Diagnostik Menurut Tarif Rumah Sakit Terhadap Biaya Paket Ina CBG'S Kanker Mammæ Per Kelas Kepesertaan Pasien.	Peneliti Utama	10. Dr. Esti Handayani, Dra., Apt., MARS
	Anggota	1. Rahayu Warni Kusasih, SKM., MM 2. Aprilia Devi Fatimah, SKM 3. Hanifa Nabila, SKM
Prevalensi Infeksi Saluran Kemih Terkait Penggunaan Kateter Pada Pasien Rawat Inap RSUD Dr. Soetomo Surabaya	Peneliti Utama	11. Deby Kusumaningrum, dr., M.Si., SpMK
	Anggota	1. Dr. Tarmono, dr., SpU(K) 2. Lusiya Ningsih, S, dr 3. Rahmad Krismantoro, dr
Korelasi Antara Pola Resistensi Flora Usus Besar, Bakteri Lingkungan Rumah Sakit dan Bakteri Penyebab Infeksi Klinik Pada Pasien di Ruang Rawat ICU RSUD Dr. Soetomo Surabaya	Peneliti Utama	12. Prof. DR. Kuntaman, dr., M.Kes., SpMK (K)
	Anggota	1. Rosantia Sarassari, dr.
Korelasi Antara Pola Resistensi Flora Usus, Bakteri Lingkungan Pasien dan Bakteri Penyebab Infeksi Klinik Pada Pasien di Ruang PICU RSUD Dr. Soetomo Surabaya (Sebuah Telaah untuk Pedoman Pencegahan Infeksi Nosokomial)	Peneliti Utama	13. Dwiyantri Puspitasari, dr., DTMH, MCTM, SpAK
	Anggota	1. Ika Nindya, dr., MMSc 2. Rosantia Sarassari, dr 3. Carrina Nenggar, dr
Prevalensi dan Pola Ventilator Associated Pneumonia di Unit Perawatan Intensif RSUD Dr. Soetomo Surabaya	Peneliti Utama	14. Bambang Pujo Semedi, dr., SpAn-KIC
	Anggota	1. Prof. Dr. Kuntaman, dr., M.Kes., Sp.MK(K) 2. Rinanti Septihingtyas, dr
Kepatuhan Penggunaan Antibiotik Profilaksis untuk Operasi Bersih di Bedah Orthopaedi RSUD Dr. Soetomo	Peneliti Utama	15. Sulis Bayusentono, dr., M.Kes., Sp.OT
	Anggota	1. Hari Paraton, Sp. OG (K) 2. Satria Ramli, dr
Pola Mikroba dan Pola Resistensi Penyebab Sepsis Pada Pasien dengan HIV/AIDS di RSUD Dr. Soetomo Surabaya	Peneliti Utama	16. Dr. Erwin Astha Triyono, dr., Sp.PD, KPTI, FINASIM
	Anggota	1. Sajuni Widjaja, dr.



Deteksi <i>Helicobacter Pylori</i> Pada Jaringan Biopsi Gaster Dengan Metode Pewarnaan Modified Giemsa Dan Warthin Starry	Peneliti Utama	17. Dr. Willy Sandhika,dr.,M.Si,Sp.PA(K)
	Anggota	1. Gilda Hartecia
Studi Pemberian Obat Kemoterapi Antibodi Monoklonal : Rituximab Pada Pasien Kemoterapi Protokol RCHOP Siklus Pertama dan Kedua (Studi Prospektif Observasional di Rawat Inap Penyakit Dalam)	Peneliti Utama	18. Novi Aryanti,S.Farm.,Apt., M.Farm.Klin
	Anggota	1. Mela Dwi Wulandari,S.Farm., Apt.,M.Farm.Klin
Uji Perbandingan Stabilitas Midazolan Hidroklorida 1 mg/ml Dalam Wadah Penyimpanan dan Suhu Berbeda	Peneliti Utama	19. Mela Dwi Wulandari,S.Farm.,Apt., M.Farm.Klin
	Anggota	1. Novi Aryanti,S.Farm.,Apt., M.Farm.Klin
Analisis Faktor Yang Mempengaruhi Lama Pelayanan Emergency di Ruang RES IGD RSUD Dr. Soetomo Surabaya	Peneliti Utama	20. Prof.Dr.H.R Eddy Rahardjo,dr.,SpAn., KIC.,KAO
	Anggota	1. Prananda Surya Airlangga,dr., M.Kes., SpAn.,KIC 2. Pesta Parulian Maurid Edward,dr., SpAn 3. Soni Sunarso Sulistiawan.,dr., SpAn.,FIPM 4. Idham Khalid,dr
Efektifitas Supervisi Kepala Ruang Terhadap Mutu Dokumentasi Asuhan Keperawatan Di RSUD Dr. Soetomo Surabaya	Peneliti Utama	21. Dewi Maryam, S.Kep.Ns,M.Kep
	Anggota	1. Kushartinah, S.Kep.Ns.M.M 2. Bambang Subagio,S.Kep.Ns.MM.Kes

Direktur RSUD Dr. Soetomo

  
dr. H. Harsono



# Molecular and Cellular Biomedical Sciences

Volume 3, Number 2, September 2019

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## RESEARCH ARTICLE

# MCBS

Mol Cell Biomed Sci. 2019; 3(2): 75-80  
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## A Comparison of Osteoblast Cell Proliferation and Osteocalcin Expression in Cuttlefish Bone and Bovine Bone Xenograft

Komang Agung Irianto<sup>1,2</sup>, Ameria Pribadi<sup>1,2</sup>, Ilham Abdullah Irsyam<sup>1,2</sup>, Yudhistira Pradnyan Klopung<sup>2</sup>, Oen Sindrawati<sup>3</sup>

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**Background:** Cuttlefish bone Xenograft, calcium phosphate (CaP)-based biomaterial graft, offers an alternative and has been accepted for osteoconductive and probable osteo-inductive attributes. This study aims to compare the bone healing potential between the bovine-derived (BHA) and cuttlefish bone-derived (CHA).

**Materials and Methods:** The study compared osteoblast cell proliferation of 27 New Zealand rabbits in 2.5 mm bone defect made in the femoral bone. The samples were divided into three groups, which were control, BHA and CHA group. The chemical and physical characteristics of BHA and CHA were determined for the content of hydroxyapatite by Fourier-Transform Infrared Spectroscopy (FTIR) and X-Ray Diffraction (XRD), then tested by Scanning Electron Microscopy (SEM) to evaluate the porosity. In the end of the second week, histopathologic and immunohistochemistry examinations were performed to evaluate the amount of osteoblast and osteocalcin expression.

**Results:** The FTIR, XRD and SEM analysis showed both BHA and CHA samples were hydroxyapatite according to Joint Committee on Powder Diffraction Standards (JCPDS). The CHA was significantly higher ( $297.22 \pm 19.772$ ) compared to BHA ( $258.22 \pm 30.926$ ) and control ( $131.67 \pm 34.213$ ). Osteocalcin expression in CHA ( $7.82 \pm 2.230$ ) compared to BHA ( $6.09 \pm 3.724$ ) and control ( $4.07 \pm 3.606$ ), was not significant ( $p > 0.05$ ).

**Conclusion:** CHA group has the highest osteoblast cell proliferation and osteocalcin expression, meaning has a good potential as future source of bone graft.

**Keywords:** cuttlefish bone, bovine, bone graft, osteoblast cell

## Introduction

Bone graft is a common technique in a bone defect to achieve secondary fracture healing where bone modelling and remodeling proceed.<sup>1</sup> An ideal graft substitute should

have bioresorbability, osteoconductive capacity, nontoxic, nonimmunogenic to the organism, easy to sterilize, and does not compromise mechanical stability.<sup>2,3</sup> Currently, autograft is the gold standard for bone graft because of its osteoconduction, osteoinduction, and osteogenesis ability.<sup>4,5</sup>

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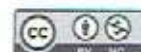
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It is, however, associated with a high morbidity and limited availability<sup>6,7</sup>, which pushes bone allografts to be used as natural substitute for bone defects<sup>1</sup>. Allograft also has a few disadvantages such as limited availability and risk of disease transmission, it presents some problems including rapid resorption, immunological rejection, infection, and technical difficulties in applying vascularized graft.<sup>5,8,11</sup> Due to the limitations of autografts and allografts, xenografts are becoming a center of focus of studies to treat bone defects.<sup>12</sup>

Xenograft has been used frequently as bone graft substitutes with good results in recent years. Xenograft should contained hydroxyapatite biomaterial or calcium phosphate based that are similar to the human bone.<sup>5</sup> Bovine bone shares the morphology, basic chemical composition, and crystallographic configuration of the mineral phase of the human bone, supporting new bone formation in contact area.<sup>7,8</sup> It has been widely-used as a bone substitute because of its osteoconductive properties. It is also less susceptible to rejection or infection.<sup>13</sup> In Indonesia, the most commonly used xenograft is bovine bone-derived.<sup>14</sup> This material has been applied successfully in bone surgeries since they combine the morphology, basic chemical composition, and crystallographic configuration of the mineral phase of the bone.<sup>15,16</sup> The use of bovine-derived xenograft (BHA) would utilize cow bones that are considered organic waste. These bovine bones have recently become a serious issue in coastal areas of Indonesia, hence a large-scale use of these otherwise useless product could contribute to a decrease in pollution in those areas.<sup>17</sup> However, the data for clinical efficacy and success rate of it is limited.<sup>18</sup>

Another xenograft that is often used is a cuttlefish bone-derived xenograft (CHA). Cuttlefish bone is a natural biomaterial consisting mainly of calcium carbonate.<sup>3</sup> It has an internal lamella matrix that is formed by an interconnected parallel sheet which creates a highly porous structure similar to coral. Previous studies have suggested the use of this material as a scaffold due to this property.<sup>10</sup> It has an advantage compared to other alternatives as it contains aragonite that could convert into hydroxyapatite when processed hydrothermally. Because of its aragonite structure, it has been featured in several studies.<sup>16,19,20</sup> It can also be obtained easily with a relatively cheap price globally. Due to its morphology and mineral structure, it can be shaped easily, hence making it compatibles with other types of bone structure with a high osteoinductive capacity.<sup>21,22</sup>

An ideal biomaterial for a scaffold should have the following characteristics: 1) High interconnected-porosity

which supports cell growth and transport of nutrition and metabolism products; 2) Mechanical capability suitable to the implantation site; 3) Chemically appropriate surface area for adhesion, proliferation, and differentiation of cells with minimal rejection from the surrounding tissue; and 4) Biocompatibility and bioresorbability with a level of degradation and resorption time similar to a natural bone tissue.<sup>23</sup>

Histologically, the fracture healing process incorporating osteoblast activation from resting state or osteogenesis from osteoprogenitor in periosteum and marrow cavity in the form of fibrocartilage callus formation. By the end of the second week, soft callus has built into hard callus as woven bone. Osteoblast cells quantity are used to examine osteoprogenitor cells differentiation capacity which indicates a progress towards physiological fracture healing.<sup>11</sup> Osteocalcin is the most abundant non-collagenous protein in mature human bone, expressed during osteoblast differentiation. It is one of the reliable markers of bone formation.<sup>12</sup>

This study would like to compare the efficacy of bone fracture healing between BHA and CHA, by evaluating the amount of osteoblast cells (the nature of osteoconductive and osteo-inductive), and osteocalcin expression (osteoblast mature differentiation) in New Zealand white rabbit.

## Materials and methods

This study was a comparative experimental study. The samples were 27 New Zealand white male rabbits each aged six to nine months, and weighed 2500 to 3000 grams. All the samples were in good health without any presence of diseases or abnormality.

The materials used were consist of a BHA processed in the Tissue Bank Laboratory of Dr. Soetomo General Hospital, Surabaya, and a CHA processed in hydrothermal reaction way in the Faculty of Science and Technology of Universitas Airlangga, Surabaya. The experimental unit used was freeze-dried hydroxyapatite xenograft pellet derived from each bone with gelatin (GEL) 10% as a binding material. To decrease the fragility of hydroxyapatite, surface modification by adding a binding material was done.<sup>24</sup>

A chemical characteristics analysis was performed in Clinical Pharmacy Laboratory of Universitas Airlangga, Surabaya, using Fourier Transform Infrared Spectroscopy (FTIR) to examine the Calcium (Ca) and Phosphorus (P) content, X-Ray Diffraction (XRD) to



examine the hydroxyapatite crystal content and Scanning Electron Microscope (SEM) to examine the porosity of each biomaterial. SEM showed pores visible with 200x magnification, the average macrospore's diameter of CHA (104.46  $\mu\text{m}$ ) and BHA (103.88  $\mu\text{m}$ ). The XRD analysis showed that the majority of samples consists of hydroxyapatite which fulfils the criteria of Joint Committee on Powder Diffraction Standards (JCPDS).

The characteristics analysis using FTIR showed an organic component with a functional group which corresponds to the wave's absorbance in a given frequency ( $\text{cm}^{-1}$ ). The FTIR spectrum of BHA showed a peak wavelength of 3396.76 whereas the spectrum of CHA showed a peak wavelength of 3311.89 and 3572.29. These indicated that CHA and BHA is a suitable hydroxyapatite based on the chemical structure of  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$  and were confirmed to be hydroxyapatite based on the criteria of JCPDS.

The study was conducted at the Institute of Tropical Disease and Laboratory of Anatomical Pathology, Faculty of Veterinary, Universitas Airlangga, Surabaya, and the ethical clearance was issued by the ethical research committee of the Faculty of Veterinary, Universitas Airlangga, Surabaya. The samples were adapted to their cages for a week before the study begins.

The rabbits were anesthetized intramuscularly on the left quadriceps muscle using atropine sulphate and diazepam. Oxytetracycline was given as a prophylactic antibiotic. Bone defects were made in each of the rabbit's distal metaphyseal region of the femur bilaterally with a 2.5 mm drill bit. The injured rabbits were then divided into the BHA group, the CHA group and the control group. The bone defect in the treatment group were implanted with bone grafts respectively according to the group. Wound care was performed on the third day and every five day afterwards.

On the end of the second week, the sample animals were sacrificed by resecting the distal femur where all samples were performed. The specimens were soaked in buffer formalin solution and slow decalcified afterwards using an acidic hydrochloric solution. The solution was changed daily until the specimens softened. A sagittal dissection was made in the affected bone and processed into paraffin block.

The hematoxylin and Eosin staining (HE) slides were further examined under the light microscope, osteoblast cells were counted for 10 fields of 40x magnification. Immunohistochemistry examination was

also prepared to evaluate the osteocalcin expression. The statistical analysis (Kruskal-Wallis and Mann-Whitney test) were performed using SPSS version 21 (SPSS Inc., Chicago, USA).

## Results

The osteoblast cell count measured from the HE-staining slides with a 40x magnification (Figure 1) showed that the CHA group have the highest number ( $297.22 \pm 19.772$ ) compared to the BHA group ( $258.22 \pm 30.926$ ) and control group ( $131.67 \pm 34.213$ ) (Table 1). According to the Kruskal-Wallis test, the difference was statistically significant ( $p < 0.001$ ).

Table 1. Osteoblast cell count comparison between groups.

Group	n	Mean	SD	p-value
Control	9	131.67	34.213	0.000*
BHA	9	297.22	19.772	
CHA	9	258.22	30.926	

Kruskal-Wallis test,  $p < 0.001$ .

Osteocalcin expression of the osteoblast cells as dark brown cytoplasmic staining were highly expressed by the CHA group calculated according to the modified Remmele method (Figure 2). The CHA group expresses the highest amount of osteocalcin ( $7.82 \pm 2.230$ ) compared to the BHA group ( $6.09 \pm 3.724$ ) and control group ( $4.07 \pm 3.606$ ). However, the difference in osteocalcin expression was not significant (Table 2).

Table 2. Osteocalcin expression comparison between groups.

Group	n	Mean	SD	p-value
Control	9	4.07	3.606	0.114
BHA	9	6.09	3.724	
CHA	9	7.82	2.230	

Kruskal-Wallis test,  $p < 0.001$ .

## Discussion

BHA is commonly used in orthopedic and dental procedure and it is commercially available. It exhibits similar properties to human bone when processed in the right temperature.<sup>13</sup> It has 75-80% porosity and a large



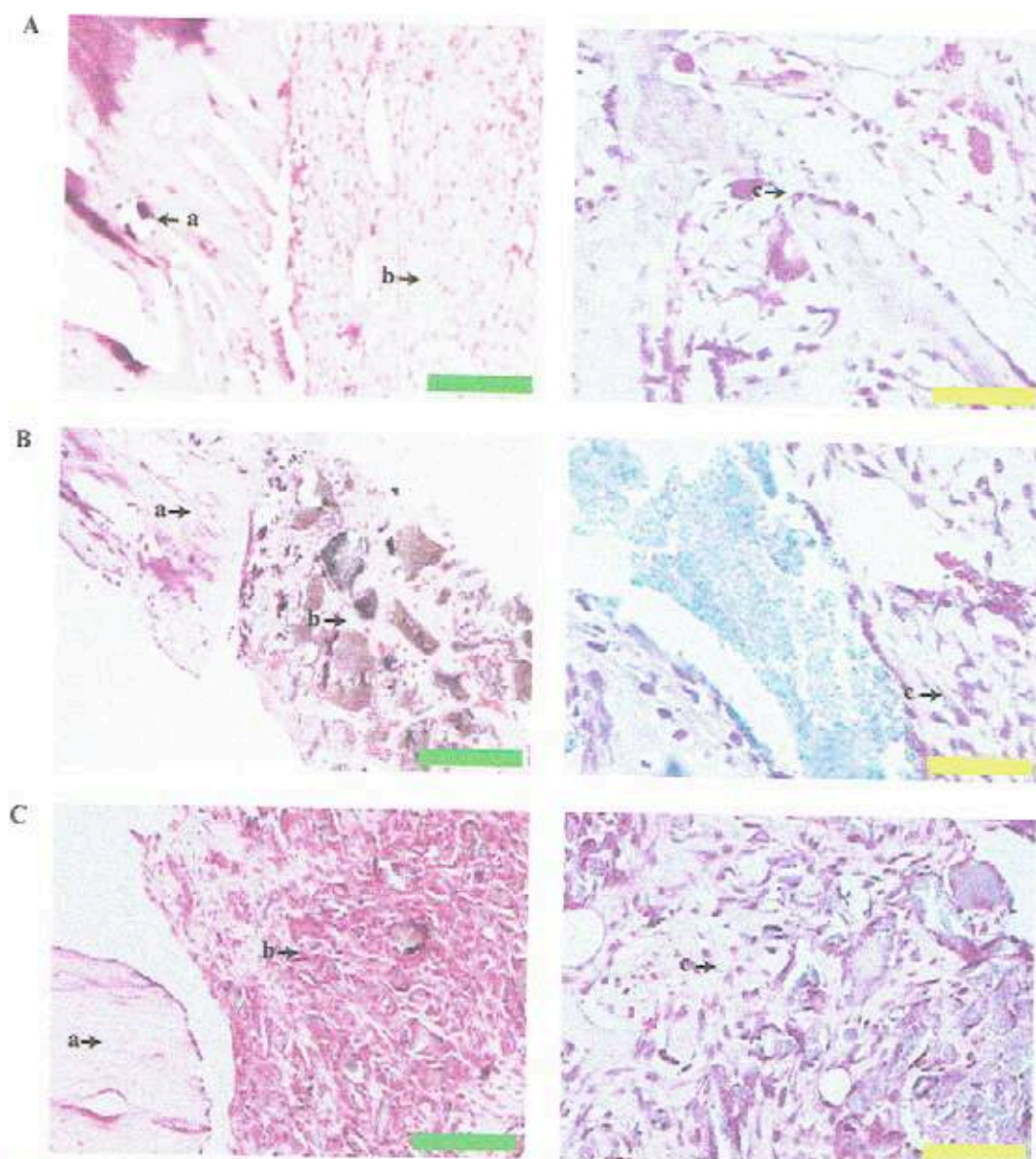


Figure 1. The histologic picture of the control (A), BHA (B) and CHA (C) group. a: cortical bone; b: fibrosis; c: osteoblastic cells; Green arrow: 10  $\mu$ m (H&E; 10x); Yellow arrow: 2.5  $\mu$ m (H&E; 40x).

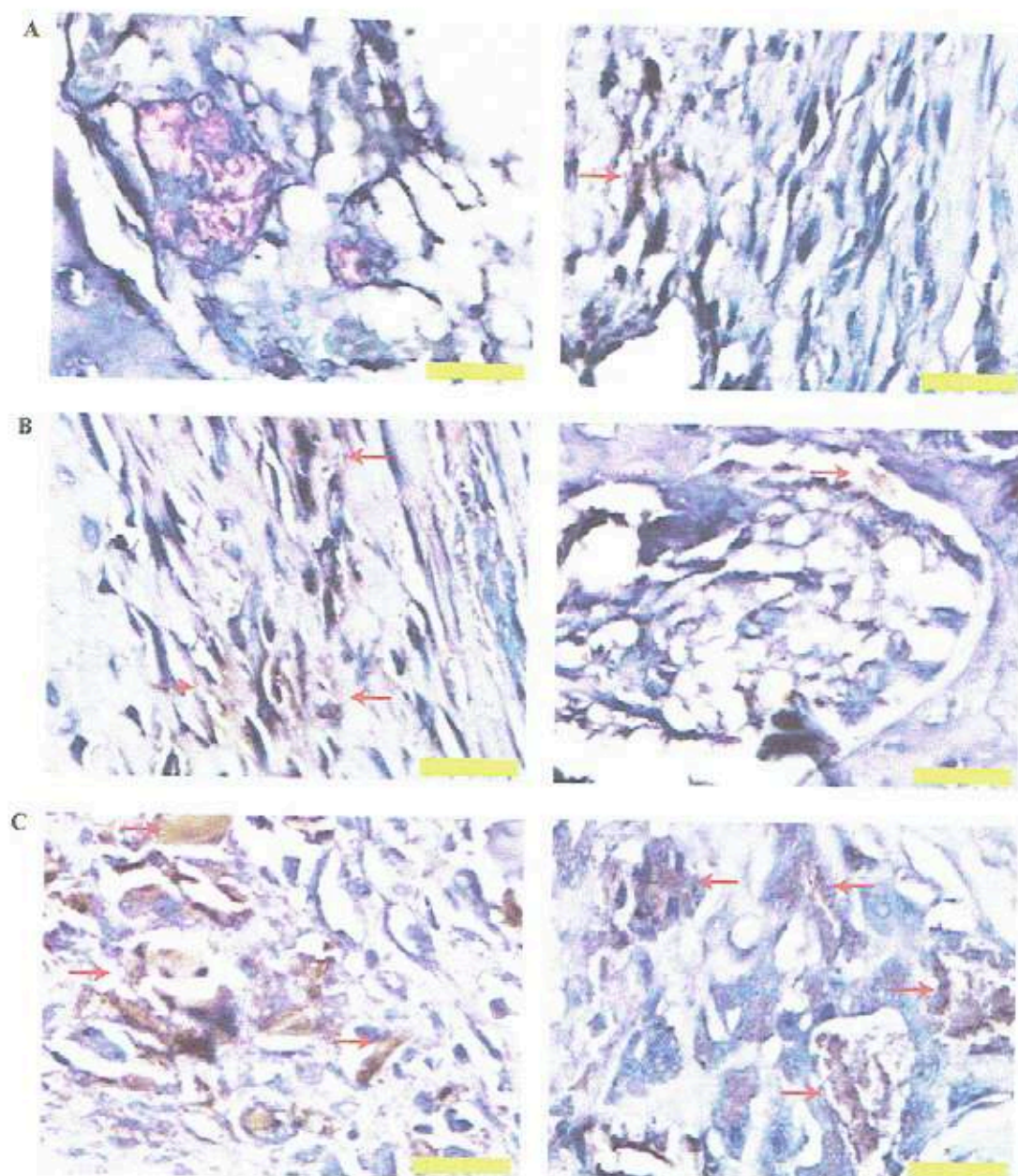
interconnecting macropore and micropore system that facilitates angiogenesis and osteoblasts migration.<sup>14</sup>

The primary constituent of cuttlefish bone is calcium carbonate.<sup>16</sup> The unique property of cuttlefish bone which has similar composition to human bones, is its high porosity which gives the cuttlefish its ability to float. Our study showed that CHA yields better osteoblast cell proliferation and higher osteocalcin production, therefore its structure is ideal as a scaffold. This is in accord with study reported by previous study which demonstrated that cuttlefish bone had excellent biocompatibility and osteogenic cell proliferation.<sup>17</sup>

The CHA is an excellent scaffold for the attachment of osteoblast activated from the resting lined in bone trabeculae and pro-osteoblast derived from progenitor in marrow. Dogan and Okumus reported cuttlefish bone graft had faster fibrous union formation during the initial week after implantation and showed better angiogenesis in the first week and by the end of observation.<sup>6</sup> The viability of the cells significantly increased in less than a week after implantation.<sup>18</sup>

The concept of osteoconduction of hydroxyapatite is well accepted while the ability for osteoinduction not to mention osteogenesis are open for discussion and further





**Figure 2.** The Immunohistochemistry staining osteocalcin expression in control group (A), BHA (B) and CHA (C) group. Red arrow: dark brown cytoplasmic staining; Yellow bar: 2.5  $\mu$ m.

research. A study found that cuttlefish bone contains other trace metals beside calcium, including magnesium.<sup>20</sup> Magnesium ions are especially important in enhancing osteoblast cell attachment to orthopedic implant.<sup>21,22</sup> Furthermore, magnesium has the ability to promote the proliferation and differentiation of osteoblast.<sup>23</sup>

In contrast to the significant higher osteoblast proliferation in CHA group, the osteocalcin expression which indicates osteoblasts maturation was not significantly

different, although still higher compared to others. The osteocalcin expression naturally showed in hard callus as it is maturing. Radiological evaluation of CHA in 3 weeks implantation showed 100% hard callus formation compare to 75% callus in BHA.<sup>6</sup>

The result in this study suggested that CHA had compatible if not superior bone regenerative capability compared to BHA. Hopefully, this material could be applied clinically in the future as it offers a cheap, abundant alternative.<sup>24,25</sup>



The authors also realized the limitations of this study. The observation made in this study was one time only, at the end of second week after implantation. Further studies should incorporate continuous observation in each following week to better observe the degree of osteoblast maturation and osteocalcin expression in different stages of healing and proceed to evaluate the remodeling process which implicate the whole fracture healing. The authors also hope with this successful animal study, future clinical human application is achievable in near future.

## Conclusion

Hydroxyapatite of the CHA yielded a higher osteoblast cell number compared to the BHA and control group. Furthermore, cuttlefish bone also presents a higher expression of osteocalcin which indicates mature osteoblast albeit insignificant statistically.

## Acknowledgements

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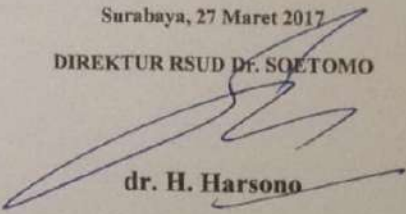
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**“Perbandingan Jumlah Osteoblast dan Alkaline Phosphatase pada Small Bone Defect Os Femur New Zealand white Rabbit Yang Diberi Cuttlefish dan Bovine Bone Xenograft “**

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