



**KEMENTERIAN RISET, TEKNOLOGI, DAN PENDIDIKAN TINGGI
UNIVERSITAS HASANUDDIN**

LEMBAGA PENELITIAN DAN PENGABDIAN MASYARAKAT (LP2M)

Jl. Perintis Kemerdekaan KM.10 Kampus UNHAS Tamalanrea Makassar 90245

Telp.(0411) 587032, 582500, 588888 Fax.(0411) 587032, 584024

Website : <http://www.unhas.ac.id/lppm> email : lp2m@unhas.ac.id

Nomor : 3516/UN4.20/TU.15/2015
Lampiran : 1 (satu) eks.
Hal : Unggah Tahapan Kegiatan Ke SIMLITABMAS

06 Juli 2015

Yth. Para Ketua Peneliti

Hibah Desentralisasi dan Kompetitif Nasional Tahun Pelaksanaan 2015

di

Makassar

Menindaklanjuti surat Ketua LP2M Unhas No. 2924/UN4.20/TU.15/2015 tentang Undangan Monev dengan ini kami sampaikan bahwa sampai saat ini tanggal 06 Juli 2015, saudara belum mengunggah laporan kemajuan dan tahapan lainnya (*laporan penggunaan anggaran dan logbook*) ke SIMLITABMAS. Untuk itu dihimbau kepada para ketua peneliti (*daftar nama terlampir*) agar dapat mengunggah laporan kemajuan dan tahapan lainnya tersebut ke SIMLITABMAS (<http://simlitabmas.dikti.go.id>) sebelum sistem tertutup.

Atas perhatiannya, kami sampaikan terima kasih.

Ketua,

Prof. Dr. Ir. Sudirman, M.Pi
NIP. 196412121989031004

Tembusan

1. Wakil Rektor 1 Unhas

Pusat Penelitian dan Pengembangan :

- Puslitbang Sumberdaya Alam
- Puslitbang Lingkungan Hidup
- Puslitbang Bioteknologi
- Puslitbang Tata Ruang dan Wilayah Informasi Spasial

- Puslitbang Biodiversity and Climate Change
- Puslitbang Kependudukan dan Gender
- Puslitbang Energi dan Ketenagalistrikan
- Puslitbang Ilmu – Ilmu Kesehatan

- Puslitbang Laut, Pesisir dan Pulau-Pulau Kecil
- Puslitbang Dinamika Masyarakat, Budaya dan Humaniora
- Pusat Desiminasi, Publikasi dan Informasi HaKI
- Laboratorium Terpadu



05-07-2015 22:15:38 Desentralisasi PTN dan PT Non Binaan melalui Tahun 2015 pelaksanaan tahun 2016 mulai tanggal 8 Juni 2015 s.d. 11 Juli 2015 Dikti.myanmar Online: 70 pengunjung.

Beranda Usulan Hibah Penilaian Monitoring Pelaksanaan Data Pendukung Pesan

Thn Pelaksanaan: 2015

Kembali

Monitoring Laporan Kemajuan

Nama PT : Universitas Hasanuddin
Kode PT : 001005
Skema hibah: Kerjasama Luar Negeri dan Publikasi Internasional

Jml data: 5, Jml baris: 10

Table with 4 columns: No, Nama Ketua - NIDN Nama Prodi, Judul, Thn Usulan, Dana Disetujui. Contains 5 rows of grant data.

SURAT PERJANJIAN PELAKSANAAN PEKERJAAN

Antara

LEMBAGA PENELITIAN DAN PENGABDIAN PADA MASYARAKAT UNHAS

Dengan

KETUA/PENANGGUNGJAWAB KEGIATAN

Nomor : 1765/UN4.20/PL.09/2015

Pada hari ini Selasa, tanggal Tiga Puluh Satu bulan Maret tahun Dua Ribu Lima Belas, kami yang bertandatangan di bawah ini :

- 1 Prof. Dr. Sudirman, M.Pi : Ketua Lembaga Penelitian dan Pengabdian Pada Masyarakat Universitas Hasanuddin, dalam hal ini bertindak untuk dan atas nama Universitas Hasanuddin selanjutnya disebut **PIHAK PERTAMA**.
- 2 dr. Upik Anderiani Miskad, Sp.PA., PhD : Ketua Pelaksana Kegiatan Penelitian Bagi Dosen Perguruan Tinggi Batch II Tahun Anggaran 2015 / Dosen Fakultas Kedokteran Universitas Hasanuddin selanjutnya disebut **PIHAK KEDUA**.

Secara bersama-sama telah sepakat mengadakan Perjanjian Pelaksanaan Hibah Penelitian antara Ketua Lembaga Penelitian dan Pengabdian Masyarakat Universitas Hasanuddin dengan Ketua Pelaksana Kegiatan tentang "Pelaksanaan Hibah Penelitian Bagi Dosen Perguruan Tinggi Batch II Tahun 2015" No. 122/SP2H/PL/DIT.LITABMAS/II/2015, tanggal 5 Februari 2015, dengan ketentuan dan syarat-syarat sebagaimana tercantum pada pasal-pasal tersebut di bawah ini:

PASAL 1

PIHAK PERTAMA memberikan tugas kepada **PIHAK KEDUA** dan **PIHAK KEDUA** menerima penyerahan dari **PIHAK PERTAMA** pelaksanaan pekerjaan tentang penelitian :

"Identify and Analyze Molecular Markers in the Progression and metastasis of colorectal cancer Evaluation of protein regenerating Liver-3 (PRL-3) as an emerging marker of carcinogenesis and its interact with other markers (Integrin B1, E Cadherin, MMP)"

PASAL 2

1. **PIHAK KEDUA** sebagai penanggungjawab kegiatan berkewajiban menyampaikan kepada **PIHAK PERTAMA** laporan hasil pelaksanaan kegiatan tersebut dan penggunaan dana beserta pembayaran pajak-pajak kegiatan paling lambat tanggal 10 November 2015.
2. **PIHAK KEDUA** wajib menyerahkan laporan hasil Program Penelitian kepada **PIHAK PERTAMA** sebanyak 3 (tiga) eksemplar beserta output penelitian (publikasi/draft publikasi, atau buku ajar/teks, poster, Teknologi Tepat Guna dan Paten serta output lainnya) dalam bentuk hard copy dan soft copy dan **PIHAK PERTAMA** mengirim langsung kepada Pejabat Pembuat Komitmen Kegiatan Subdit Penelitian Direktorat Penelitian dan Pengabdian Masyarakat, Direktorat Jenderal Pendidikan Tinggi Kementerian Pendidikan dan Kebudayaan, selaku pemberi dana, dan menyerahkan 2 (dua) eksemplar sebagai arsip pada Lembaga Penelitian dan Pengabdian Masyarakat Universitas Hasanuddin.

PASAL 3

Jangka waktu pelaksanaan kegiatan tersebut selama 10 (sepuluh) bulan terhitung sejak tanggal 05 Februari 2015 sampai dengan tanggal 10 November 2015.

PASAL 4

1. **PIHAK PERTAMA** menyalurkan dana Hibah Penelitian Bagi Dosen Perguruan Tinggi Batch II dari pihak pemberi pekerjaan yang tersebut pada pasal 1 sebesar Rp. 172.500.000,- (Seratus Tujuh Puluh Dua Juta Lima Ratus Ribu Rupiah) yang dibebankan pada DIPA Direktorat Penelitian dan Pengabdian Masyarakat Tahun Anggaran 2015, nomor DIPA-023.04.1.673453/2015 Tanggal 14 November 2014, DIPA Revisi 01 Tanggal 03 April 2015 yang akan dibayarkan dalam 2 (dua) tahap dan ditransfer melalui rekening masing-masing pada BNI 1946 Capem Unhas Tamalanrea, dengan rincian sebagai berikut :
 1. Tahap I Rp 172,500,000 x 70% Rp 120,750,000
 2. Tahap II Rp 172,500,000 x 30% Rp 51,750,000
2. Bahwa sesuai dengan ketentuan yang berlaku di Universitas Hasanuddin dana penelitian dikenakan biaya institutional fee

PASAL 5

1. Penerimaan dana Tahap I dilakukan setelah PIHAK KEDUA menyerahkan revisi proposal dan revisi anggaran
2. Penerimaan dana Tahap II akan dilakukan jika syarat-syarat yang tertuang pada pasal 2 dan syarat administrasi lainnya sesuai aturan yang berlaku di Universitas Hasanuddin dapat dipenuhi.
3. Apabila dalam batas waktu yang telah ditetapkan, PIHAK KEDUA tidak segera menyerahkan laporan hasil kegiatan tersebut kepada PIHAK PERTAMA, maka PIHAK KEDUA dikenakan denda satu perseribu setiap hari keterlambatan, terhitung dari tanggal jatuh tempo yang telah ditetapkan sampai setinggi-tingginya 5% (lima persen) dari Harga/Nilai Perjanjian (Kontrak).
4. Ketua Pelaksana Kegiatan yang tidak menyerahkan laporan hasil kegiatannya dalam akhir tahun anggaran yang sedang berjalan dalam waktu proses pencairan biayanya telah berakhir maka seluruh biaya yang bersangkutan yang belum sempat dicairkan dinyatakan hangus (tidak dapat dicairkan kembali)
5. Apabila PIHAK KEDUA tidak dapat memenuhi perjanjian pelaksanaan kegiatan ini, maka PIHAK KEDUA wajib mengembalikan kepada PIHAK PERTAMA dana kegiatan yang telah diterimanya, untuk selanjutnya disetorkan kembali ke Kas Negara

PASAL 6

1. Apabila PIHAK KEDUA, karena satu dan lain hal bermaksud merubah pelaksanaan/lokasi/jangka waktu/ketua pelaksana dari pelaksanaan kegiatan yang telah disepakati dalam Surat Perjanjian ini PIHAK KEDUA harus mengajukan permohonan perubahan tersebut kepada PIHAK PERTAMA
2. Perubahan pelaksanaan/lokasi/jangka waktu/ketua pelaksana tersebut dapat dibenarkan bila telah mendapat persetujuan secara tertulis terlebih dahulu dari PIHAK PERTAMA

PASAL 7

Hak Cipta Kegiatan tersebut berada pada Ketua Pelaksana Kegiatan, sedangkan untuk penggandaan/memperbanyak laporan akhir hasil kegiatan adalah wewenang pelaksana.

PASAL 8

Surat Perjanjian Pelaksanaan Kegiatan ini, ditandatangani oleh kedua belah pihak di Makassar pada hari dan tanggal tersebut di atas dan dibuat rangkap dua.

PASAL 9

Hal-hal yang belum diatur dalam perjanjian ini akan ditentukan kemudian oleh kedua belah pihak secara musyawarah

PIHAK KEDUA,

dr. Upik Anderiani Miskad, Sp.PA., PhD



PIHAK PERTAMA,



Prof. Dr. Sudirman, M.Pi
NIP. 19641212.198903.1.004

SURAT KETERANGAN TANGGUNGJAWAB MUTLAK

Yang bertandatangan di bawah ini :

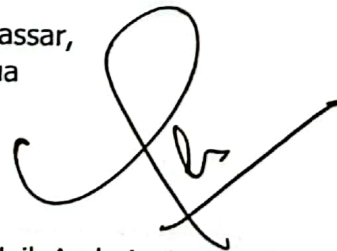
Nama : dr. Upik Anderiani Miskad, S.Ked., Ph.D
Jabatan : Ketua Tim/Dosen Fak. Kedokteran Unhas

Menyatakan bahwa :

1. Saya telah menerima dana tahap II Program Penelitian Bagi Dosen Perguruan Tinggi tahun 2015 sebesar Rp. 49.162.500,- (Empat Puluh Sembilan Juta Seratus Enam Puluh Dua Ribu Lima Ratus Rupiah) dan menggunakannya sesuai dengan peruntukannya
2. Saya bertanggungjawab penuh atas pengelolaan administrasi keuangan kegiatan tersebut sesuai dengan peraturan perundang-undangan yang berkaitan dengan pengelolaan keuangan pemerintah yang berlaku dan berdasarkan persetujuan anggaran sebagaimana yang dituangkan dalam surat perjanjian kerjasama antara Pejabat Pembuat Komitmen Kegiatan Subdit Penelitian Direktorat Penelitian dan Pengabdian Masyarakat, Direktorat Jenderal Pendidikan Tinggi Kementerian Pendidikan dan Kebudayaan dengan Ketua LP2M Universitas Hasanuddin tentang "Pelaksanaan Program Penelitian Bagi Dosen Perguruan Tinggi Tahun 2015" No. 122/SP2H/PL/DIT.LITABMAS/II/2015, tanggal 5 Februari 2015 untuk kegiatan "Identify and Analyze Molecular Markers in the Progression and metastasis of colorectal cancer Evaluation of protein regenerating Liver-3 (PRL-3) as an emerging marker of carcinogenesis and its interact with other markers (Integrin B1, E Cadherin, MMP"
3. Menyampaikan laporan keuangan secara rutin kepada Pejabat Pembuat Komitmen selaku pemberi dana dan Lembaga Penelitian dan Pengabdian Masyarakat Unhas sebagai institusi penanggungjawab kegiatan
4. Bersedia diperiksa oleh aparat pemeriksa fungsional bilamana diperlukan.
5. Mengarsipkan semua dokumen keuangan secara tertib dan teratur

Demikian surat keterangan tanggungjawab mutlak ini dibuat dengan sebenarnya untuk dipergunakan seperlunya

Makassar,
Ketua



dr. Upik Anderiani Miskad, S.Ked., Ph.D



**KEMENTERIAN PENDIDIKAN DAN KEBUDAYAAN
UNIVERSITAS HASANUDDIN
LEMBAGA PENELITIAN DAN PENGABDIAN MASYARAKAT (LP2M)**

Jl. Perintis Kemerdekaan KM.10 Kampus UNHAS Tamalanrea Makassar 90245

Telp.(0411) 587032, 582500, 588888 Fax.(0411) 587032, 584024

Website : <http://www.unhas.ac.id/lppm> email : lp2m@unhas.ac.id

Nomor : 4126 /UN4.20/UM.13/2014
Lampiran : 3 (tiga) lembar
Hal : **Evaluasi Kelayakan Penelitian Hibah Desentralisasi
Dan Kompetitif Nasional 2014-2015**

23 Oktober 2014

Yth. Para Ketua Peneliti Hibah Desentralisasi dan Kompetitif Nasional (Daftar NamaTerlampir)

di

Makassar

NO	URAIAN	JUMLAH	KETERANGAN
1.	Bersama ini terlampir kami kirimkan surat dari Kementerian Pendidikan dan Kebudayaan Direktorat Jenderal Pendidikan Tinggi No.3343/E5.2/PL/2014 Tanggal 21 Oktober 2014 perihal Penetapan Evaluasi Kelayakan	3 (tiga) lembar	Disampaikan dengan hormat untuk diketahui.

a.n. Ketua,

Sekretaris

Prof. Dr. Armin, M.Si
NIP. 196511041991031008

Tembusan :

1. Wakil Rektor 1 Unhas
2. Ketua LP2M Unhas

Pusat Penelitian dan Pengembangan :

- Puslitbang Sumberdaya Alam
- Puslitbang Lingkungan Hidup
- Puslitbang Bioteknologi
- Puslitbang Tata Ruang dan Wilayah Informasi Spasial

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- Puslitbang Ilmu - Ilmu Kesehatan

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- Pusat Desiminasi, Publikasi dan Informasi MaKI
- Laboratorium Terpadu



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UNIVERSITAS HASANUDDIN
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Jl. Perintis Kemerdekaan KM.10 Kampus UNHAS Tamalanrea Makassar 90245

Telp.(0411) 587032, 582500, 588888 Fax.(0411) 587032, 584024

Website : <http://www.unhas.ac.id/lppm> email : lp2m@unhas.ac.id

Lampiran Surat No. 4126 /UN4.20/UM.13/2014

NO	NAMA	FAKULTAS	NAMA SKIM	PELAKSANA
1	Juanda Nawawi	Isipol	Unggulan Perguruan Tinggi	Perguruan Tinggi
2	Danial Rahim	Pertanian	Unggulan Perguruan Tinggi	
3	Musrizal Muin	Kehutanan	Unggulan Perguruan Tinggi	
4	Intan Sari Dewi	Teknik	Unggulan Perguruan Tinggi	
5	Syamsuddin Garancang	Peternakan	Unggulan Perguruan Tinggi	
6	Syamsuddin Hasan	Peternakan	Unggulan Perguruan Tinggi	
7	Andi Detty Yunianti	Kehutanan	Unggulan Perguruan Tinggi	
8	Jumriah Langkong	Pertanian	Unggulan Perguruan Tinggi	
9	Syafaruddin	Teknik	Unggulan Perguruan Tinggi	
10	Daeng Paroka	Teknik	Unggulan Perguruan Tinggi	
11	Dewiani	Teknik	Unggulan Perguruan Tinggi	
12	Rindam Latif	Pertanian 1	Unggulan Perguruan Tinggi	
13	Andi Nasruddin	Pertanian 2	Unggulan Perguruan Tinggi	
14	Jeanny Maria Fatimah	Isipol	Unggulan Perguruan Tinggi	
15	Mufidah	Farmasi	Unggulan Perguruan Tinggi	
16	Bachrul Ibrahim	Pertanian	Unggulan Perguruan Tinggi	
17	Jasmal Ahmari Syamsu	Peternakan	Unggulan Perguruan Tinggi	
18	Syahrani Syahrir	Peternakan	Unggulan Perguruan Tinggi	
19	Ria Wikantari	Teknik	Unggulan Perguruan Tinggi	
20	Aminuddin	Hukum	Unggulan Perguruan Tinggi	
21	Meta Mahendradatta	Pertanian	Unggulan Perguruan Tinggi	
22	Djoni Prawira	Peternakan	Unggulan Perguruan Tinggi	
23	Hafied Cangara	Isipol	Unggulan Perguruan Tinggi	
24	Faisal	Teknik	Unggulan Perguruan Tinggi	
25	Mariaty Bilang	Pertanian	Unggulan Perguruan Tinggi	
26	Sudirman	Peternakan	Unggulan Perguruan Tinggi	
27	Yushinta Fujaya	IKP	Unggulan Stranas	Ditlitabmas
28	Baharuddin	Pertanian	Unggulan Stranas	
29	Abubakar Tawali	Pertanian	Unggulan Stranas	
30	Upik Anderiani Miskad	Kedokteran	KLN	
31	Rohani AR	IKP	KLN	
32	Rudi Jamaluddin	Teknik	KLN	
33	Maming	MIPA	Stranas	
34	Ratmawati Malaka	Peternakan	Stranas	
35	Andi Niartiningsih	IKP	Stranas	
36	Juhriah	MIPA	Stranas	
37	Asmuddin Natsir	Peternakan	Stranas	
38	Muhammad Irfan Said	Peternakan	Stranas	
39	Nursini	Ekonomi	Stranas	
40	Hamzah	IKP	Stranas	
41	Suhasman	Kehutanan	Stranas	
42	Muhammad Ichsan AD	Peternakan	Stranas	
43	Tasrief Surungan	MIPA	Hikom	

Pusat Penelitian dan Pengembangan :

- Puslitbang Sumberdaya Alam
- Puslitbang Lingkungan Hidup
- Puslitbang Bioteknologi
- Puslitbang Tata Ruang dan Wilayah Informasi Spasial

- Puslitbang Biodiversity and Climate Change
- Puslitbang Kependudukan dan Gender
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- Puslitbang Dinamika Masyarakat, Budaya dan Humaniora
- Pusat Desiminasi, Publikasi dan Informasi HaKI
- Laboratorium Terpadu






**KEMENTERIAN PENDIDIKAN DAN KEBUDAYAAN
UNIVERSITAS HASANUDDIN
LEMBAGA PENELITIAN DAN PENGABDIAN MASYARAKAT (LP2M)**

Jl. Perintis Kemerdekaan KM.10 Kampus UNHAS Tamalanrea Makassar 90245

Telp.(0411) 587032, 582500, 588888 Fax.(0411) 587032, 584024

Website : <http://www.unhas.ac.id/lppm> email : lp2m@unhas.ac.id

44	Mukti Zainuddin	IKP	Hikom	Ditlitabmas
45	Sumbangan baja	Pertanian	Hikom	
46	Pawennari Hijjang	Isipol	Hikom	
47	Itji Diana Daud	Pertanian	RAPID	
48	Sitti Bulkis	Pertanian	MP3EI	
49	Tamrin	Pertanian	MP3EI	
50	Ade Rosmana	Pertanian	MP3EI	
51	Indah Raya	MIPA	MP3EI	
52	Zainal	Pertanian	MP3EI	
53	Tutik Kuswinanti	Pertanian	MP3EI	
54	Amran Laga	Pertanian	MP3EI	
55	Muhammad W. Tjaronge	Teknik	MP3EI	
56	Saadah	Pertanian	MP3EI	
57	A. Nixia Tenriawaru	Pertanian	MP3EI	
58	Andi Haris Muhammad	Teknik	MP3EI	
59	Muhammad Farid BDR	Pertanian	MP3EI	
60	Hilal Anshary	IKP	MP3EI	
61	Sartini	IKP	MP3EI	

dan Ketua,
Sekretaris

Prof. Dr. Armin, M.Si
NIP. 196511041991031008

Pusat Penelitian dan Pengembangan :

- Puslitbang Sumberdaya Alam
- Puslitbang Lingkungan Hidup
- Puslitbang Bioteknologi
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- Puslitbang Dinamika Masyarakat, Budaya dan Humaniora
- Pusat Desiminasi, Publikasi dan Informasi HAKI
- Laboratorium Terpadu

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**KEMENTERIAN PENDIDIKAN DAN KEBUDAYAAN
DIREKTORAT JENDERAL PENDIDIKAN TINGGI**

Jalan Jenderal Sudirman, Pintu I Senayan, Jakarta 10270
Telepon (021) 57946100 Ext. 0433 Faximili (021) 5731846
Laman <http://dikti.go.id>

Nomor : 3343/E5.2/PL/2014
Hal : Penetapan Evaluasi Kelayakan

21 Oktober 2014

Yth. Ketua LP/LPPM
Perguruan Tinggi Negeri dan Swasta
di Indonesia

Menindaklanjuti surat kami nomor 0728/E5.1/PE/2014 tanggal 4 Maret 2014, perihal jadwal pelaksanaan penugasan program penelitian, PPM dan PKM di Perguruan Tinggi serta berdasarkan hasil monitoring dan evaluasi Penelitian Program Desentralisasi dan Kompetitif Nasional ke Perguruan Tinggi, yang dilaksanakan bulan September 2014 oleh Direktorat Penelitian dan Pengabdian kepada Masyarakat Ditjen Pendidikan Tinggi, dengan hormat kami informasikan bahwa Direktur Penelitian dan Pengabdian kepada Masyarakat telah menetapkan nama-nama peneliti yang lolos untuk mengikuti seminar evaluasi kelayakan sebagaimana daftar terlampir.

Para peneliti dimaksud dimohon segera mengunggah proposal lanjutan paling lambat tanggal 27 Oktober 2014 sudah masuk di SIM-LITABMAS untuk digunakan sebagai persyaratan mengikuti Seminar Evaluasi Kelayakan yang akan dilaksanakan dalam waktu dekat ini.

Sesuai Panduan Pelaksanaan Penelitian dan Pengabdian kepada Masyarakat di Perguruan Tinggi Edisi IX pelaksanaan Seminar Evaluasi Kelayakan mengikuti ketentuan sebagaimana diatur pada tabel berikut:

No.	PROGRAM HIBAH	STATUS PT	KELOMPOK	PELAKSANA EVALUASI KELAYAKAN
1	Kompetitif Nasional (PUSNAS, KLN, STRANAS, HIKOM, RAPID, MP3EI)	PTN dan PTS		Dititabmas
2	Desentralisasi (PUPT, PPS, PF, PHB, PEKERTI)	PTS	Binaan	Dititabmas
		PTN dan PTS	Mandiri, Utama, dan Madya	Perguruan Tinggi
		PTN	Binaan	

Perlu kami sampaikan bahwa pelaksanaan Seminar Evaluasi Kelayakan harus sudah diselesaikan paling lambat tanggal 22 Nopember 2014.

Demikian disampaikan atas perhatian dan kerjasamanya kami sampaikan terima kasih.

Direktur Penelitian dan
Pengabdian kepada Masyarakat,

Ttd,

Agus Subekti
NIP 196008011984031002

Tembusan:

1. Dirjen Pendidikan Tinggi
2. Rektor Perguruan Tinggi
3. Koordinator Perguruan Tinggi Swasta Wilayah I-XII

Code/ Field of Science: 306/ Basic Medical Science

**FINAL REPORT SECOND YEAR
INTERNATIONAL RESEARCH COLLABORATION
AND SCIENTIFIC PULICATION**



**IDENTIFY AND ANALYZE MOLECULAR MARKERS IN THE
PROGRESSION AND METASTASIS OF COLORECTAL CANCER;**

Evaluation of Protein Regenerating Liver-3 (PRL-3) as an emerging marker of carcinogenesis and its interact with other markers (Integrin β 1, E Cadherin, MMP2, MMP9, VEGF A, VEGF C and EGFR)

PRINCIPAL INVESTIGATOR:

1. dr. Upik A. Miskad, PhD, SpPA (NIDN:0030037403)
2. dr. M. Husni Cangara, Ph.D (NIDN 0009047705)
3. Prof. dr. Syarifuddin Wahid, Ph.D, SpPA(K) (NIDN 0024074402)
4. Prof. Alfred Lam, MD, PhD (Griffith University Australia)

**HASANUDDIN UNIVERSITY
GRIFFITH UNIVERSITY
NOVEMBER 2015**

Code/ Field of Science: 306/ Basic Medical Science

**PROGRESS REPORT
INTERNATIONAL RESEARCH COLLABORATION
AND SCIENTIFIC PULICATION**



**IDENTIFY AND ANALYZE MOLECULAR MARKERS IN THE
PROGRESSION AND METASTASIS OF COLORECTAL CANCER;**

Evaluation of Protein Regenerating Liver-3 (PRL-3) as an emerging marker of carcinogenesis and its interact with other markers (Integrin β 1, E Cadherin, MMP2, MMP9, VEGF A, VEGF C and EGFR)

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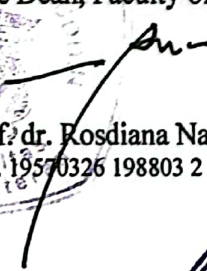
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ABSTRACT

Background. Colorectal cancer is the third most common malignant neoplasm worldwide and the second leading cause of death due to cancer in the United States. In Indonesia, colorectal cancer is an emerging public health problem and currently ranks among the three highest cancers. In Makassar, South Sulawesi Indonesia, the incidence of colorectal cancer is increasing and recorded as the most common malignant cancer according the pathology based data during 2010-2011. Despite recent advances in diagnostic and therapeutic measures develop, the prognosis of colorectal cancer patients with distant metastasis still remains poor. Mortality rate of colorectal cancer quite high and related to metastasis. Study on molecular carcinogenesis in colorectal cancer among Indonesian population is still few, therefore, it is necessary to clarify the molecular mechanisms involved in development and metastasis and to identify the specific biomarkers of colorectal cancer metastasis. Recently *PRL-3 (phosphatase of regenerating liver-3/PTP4A3)* was reported participates in invasion, migration, metastasis and angiogenesis. But the cascade and which molecular interact with this protein still need to identify.

Material and methods. Tissue samples approximately 100 cases were collected from the patients with colorectal cancer in Hasanuddin University Hospital and Wahidin Sudirohusodo Hospital. The clinicohistopathological data were recorded and the expression of protein PRL-3, E Cadherin, MMP2 and MMP9 were detected by immunohistochemistry and analyzed molecular interact between them.

Results. PRL-3 protein was detected in cytoplasmic and cytoplasmic membrane of cancer cell. The expression was various among tumor cell.

Keywords: Colorectal Cancer, PRL-3, E Cadherin, MMP2, MMP9, marker carcinogenesis, metastasis

CHAPTER I
INTRODUCTION

I.1 BACKGROUND

Colorectal cancer is the third most common malignant neoplasm worldwide (Shike M, 1990) and the second leading cause of death due to cancer in the United States (Winawer SJ, 1997). In Indonesia, colorectal cancer is an emerging public health problem and currently ranks among the three highest cancers (Murdani, 2012). In Makassar, South Sulawesi Indonesia during 2010-2011, the incidence of colorectal cancer is increasing and recorded as the most common malignant cancer in Makassar according the pathology based data.

Lack of a colonoscopy screening and lifestyle changes might contribute to it. Diet is clearly implicated in the origin of colorectal cancer, with risk factors for the disease including reduced consumption of vegetables, fiber, and starch and increased consumption of red meat and animal fat. Several hypotheses have been developed to explain these associations (Bruce WR, 2000). High consumption of meat was found in Makassar population since the famous food in Makassar is a meat soup containing mostly gut. Although this lifestyle may contribute to many disease including cancer, but there is no study about correlation between dietary style and development of colorectal cancer in this population.

In the last few decades, there is an increasing interest towards the contribution of genetic-environment interaction in colorectal carcinogenesis. Some studies have indicated that CRC might develop through several different pathways; the three major routes are chromosomal instability (CIN), microsatellite instability (MSI), and inflammatory pathways. An earlier study on clinical epidemiology of CRC in Indonesia showed that the majority of patients were diagnosed between 45 and 50 years old, with a mean age around 47 years old. It is affect more younger population compare to other countries reported. Study on molecular carcinogenesis in colorectal cancer among Indonesian population is still few and need more study to elaborate clinical and pathological as well as molecular marker in colorectal cancer (Murdani, 2012). Despite recent advances in diagnostic and therapeutic measures develop, the prognosis of colorectal cancer patients with distant metastasis still remains poor. In addition, not a few colorectal cancer patients suffer from the unexpected development of occult metastases, especially in the liver and lung, after the curative resection of their primary tumors. Commonly in Indonesia, the patient with colorectal cancer come to see the clinician when the condition is already advanced stage. Mortality rate of colorectal cancer quite high and related to metastasis. Therefore, it is necessary to clarify the molecular mechanisms involved in metastasis and to identify the specific biomarkers of colorectal cancer metastasis.

To identify the consistent genetic alterations associated with the transition from primary colorectal cancers to liver metastases, (Saha *et al.* 2001) performed global gene expression profiles using a serial analysis of gene expression approach and found that *PRL-3* (*phosphatase of regenerating liver-3/PTP4A3*) was frequently overexpressed in the liver metastases studied, but expressed at lower levels in primary tumors and normal colorectal epithelium. Recently PRL-3 was reported participates in invasion, migration, metastasis and angiogenesis (Miskad UA, 2004, 2007), but the cascade and which molecular interact with this protein still need to identify.

I.2. RESEARCH RECORD

We started to study this PRL-3 gene and protein in 2003 and already published several paper in International journal, cited by other researchear. On the first time, we just checked the expression of PRL-3 protein in gastric cancer. It has been found that this gene has correlated with progression and metastasis of gastric cancer using sample from Japanese population. In Indonesia, gastric cancer is very few compared with colorectal cancer. Surgical operation with gastric cancer is limited. Meanwhile incidence of colorectal cancer increasing in Indonesian population. To the next future, we use colorectal cancer cases to understand the molecular mechanism of PRL-3.

I.3. RESEARCH OBJECTIVE

To understand the molecular mechanism of PRL-3 induce metastasis in colorectal cancer.

1. To identify the expression of PRL-3 gene and protein in colorectal cancer (primary tumor and metastasized colorectal cancer to lymphonode and liver).
2. To identify the expression of E Cadherin, Matrix Metallo Proitenase (MMP) 2 , MMP 9 in colorectal cancer.
3. To correlate the expression of PRL-3 with E Cadherin, Matrix Metallo Proitenase (MMP2) in colorectal cancer.
4. To analyse the expression of all these protein and clinicopathological parameters of colorectal cancer.

CHAPTER II

LITERATURE REVIEW

II.1 COLORECTAL CANCER

Colorectal cancer is the third most common type of cancer diagnosed in the United States and is the third most common cause of cancer-related death (Shike M, 1990). The majority of cases are sporadic, with hereditary colon cancer contributing up to 15% of all colon cancer diagnoses.

There are many known risk factors for sporadic CRC, including nonmodifiable and modifiable variables. Preventive measures should be targeted at tobacco use, dietary habits, and weight control. The inflammatory bowel disease (IBD) population is the second major category of patients at increased risk of CRC. The 2 main syndromes accounting for the inherited cases are hereditary nonpolyposis colon cancer (HNPCC) and familial adenomatous polyposis (FAP). The prevalence of HNPCC, is estimated to be 2% to 5%. The syndrome is caused by a germline mutation in 1 of 6 currently identified DNA mismatch repair (MMR) genes: *hMSH2*, *hMLH1*, *hPMS1*, *hPMS2*, *hMSH3*, and *hMSH6*. Inactivation of these genes leads to the development of short repeats of DNA, known as microsatellites; 90% of the mutations in the MMR genes are found specifically in *hMSH2* and *hMLH1*. Patients with HNPCC have an 80% lifetime risk of developing CRC. HNPCC is differentiated from sporadic colon cancer by a distinctive clinical picture. The average age of cancer diagnosis is much earlier (ie, 47 y vs 63 y), and there is a pattern of both metachronous and synchronous colon cancers, in addition to a high association with other primary tumors (eg, endometrial, ovarian, gastric, small bowel).

Initiation of colon cancer screening in the average-risk patient is indicated at age 50; however, current screening guidelines do not clearly define the optimal modality to perform screening. Sporadic colon cancer is believed to develop from benign lesions that deteriorate into carcinoma over a period of time, thus providing a window for early detection and treatment with the goal of lowering mortality. Between 1975 and 2000, the incidence of colon cancer decreased by 22%, with half of that volume attributed to screening and half to risk-factor modification and improved treatment. The screening methods for CRC are differentiated between detection and prevention. Fecal occult blood testing (FOBT) and stool DNA testing are methods that detect malignant disease, whereas computed tomography (CT) colonography, sigmoidoscopy, and colonoscopy can detect premalignant lesions (Winawer SJ, 1997).

Sporadic CRC is postulated to follow the adenoma–carcinoma sequence, precipitated by cumulative genetic mutations. Point mutations, altered DNA methylation, gene rearrangements, amplifications, and deletions comprised the most common mutational events that led to 3 described pathways leading to tumorigenesis: (1) gain of function (oncogene activation); (2) loss of function (tumor suppressors/apoptotic pathways); and (3) epigenetic alterations (DNA methylation patterns) (Sarah et al, 2011). CRC is diagnosed either after routine screening or prompted by the onset of new symptoms. Symptoms in CRC are nonspecific and vague, and may include a change in bowel habits, weight loss, abdominal pain, and fatigue. More specific symptoms such as obstruction, bleeding, or perforation may occur, prompting an urgent surgery. The goal of preoperative imaging is to accurately stage patients.

The critical component that determines prognosis in colon cancer remains the pathologic stage (Table 1). The variation in survival between early- and late-stage colon cancer underscores the importance of screening and early diagnosis. One well-known biomarker, carcinoembryonic antigen (CEA), is traditionally used postoperatively to monitor for recurrence. It has been suggested that preoperative CEA be incorporated into the TNM staging system for CRC (Sobin LH, 1997).

Table 1: TNM Staging System for Colorectal Cancer

Primary tumor (T)	
T _x	Tumor cannot be assessed
T _{is}	Carcinoma in situ
T ₁	Tumor invades submucosa
T ₂	Tumor invades muscularis propria
T ₃	Tumor invades subserosa
T ₄	Tumor directly invades adjacent organs/structures or through the visceral peritoneum

CHAPTER III
RESEARCH METODOLOGY

III.1. MATERIALS

Tissue samples. One hundred Paraffin-embedded surgical specimens of primary human colorectal carcinomas, lymph node metastases and liver metastasis were collected from Hasanuddin University Hospital and Wahidin Sudirohusodo Hospital. Informed consent was obtained from all patients. They consisted of men and women with an age range variably. Tumor size was divided in to two group according to maximum diameter. Histological type was classified as follows: well-differentiated tubular adenocarcinoma, moderately differentiated tubular adenocarcinoma, poorly differentiated adenocarcinoma, and mucinous adenocarcinoma. Depth of carcinoma invasion was classified as follows: *T1*, mucosa (m) and submucosa (sm); *T2*, muscularis propria (mp) and subserosa (ss); *T3*, serosa-exposed (se); *T4*, serosa-infiltrating (si). Extent of lymph node metastasis was classified as follow: *N0*, no evidence of lymph node metastasis; *N +* metastasis to lymph nodes; *M+* metastasis to Liver.. Lymphatic invasion, venous invasion and tumor stage was also defined for clinicopathological features.

Blood Samples. Blood samples from patient with colorectal cancer were collected. These samples were storage in -80 degrees C.

III.2. METHODS

Immunohistochemistry

Consecutive 4 μm sections were cut from each block, deparaffinized with xylene and rehydrated with graded ethanol solutions in deionized distilled water. Serial sections were subjected to hematoxylin and eosin staining to determine histological diagnoses and the remaining sections were processed for the immunohistochemical study. Immunohistochemical staining was performed using the streptavidin-biotin-peroxidase method with labeled streptavidin-biotin (LSAB; Dako, Kyoto, Japan). Briefly, the sections were placed in a glass box filled with 10 mmol/L citrate buffer (pH 6.0), and were autoclaved for 15 min at 125°C. The sections were allowed to cool in the box at room temperature (24°C) for 60 min before being immersed for 15 min in 0.3% H_2O_2 to block endogenous peroxidase, and then for 30 min in avidin-biotin blocking solution to block avidin in the tissue. The monoclonal antibodies, anti-PRL-3 (1 : 100 dilution, Attogen Bio, anti E cadherin antibody (DAKO), anti MMP2 antibody (R &D) and anti MMP9 antibody (R &

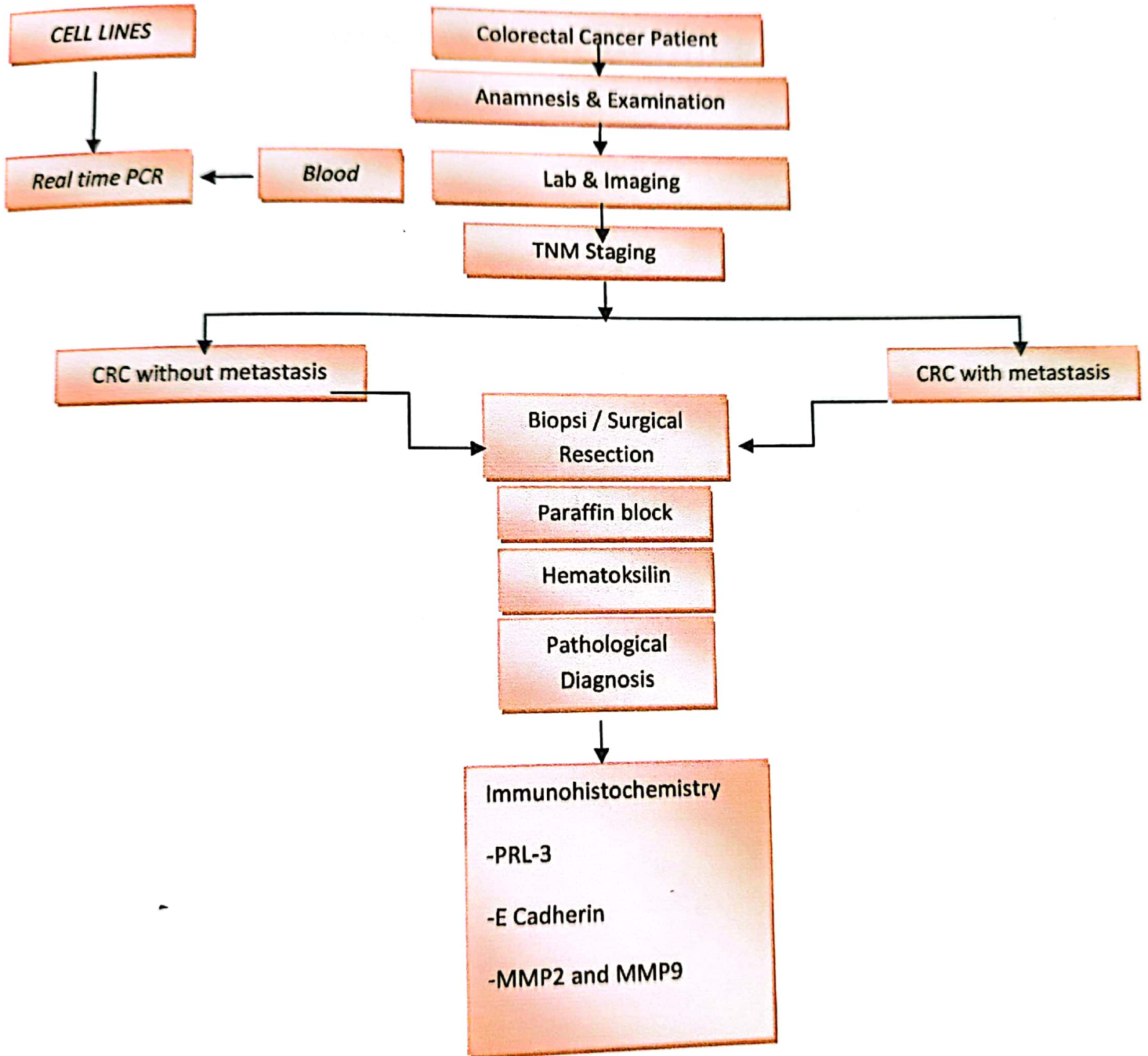
D), were applied to sections and incubated overnight at 4°C in a moist chamber. Subsequently, sections were biotinylated with goat antirabbit IgG for 30 min and streptavidin conjugated to horseradish peroxidase (DAKO, Kyoto, Japan) for 30 min. Chromogenic fixation was carried out by immersing the sections in the solution of 3,3-diamino-benzidine tetrahydrochloride (DAB) at room temperature (24°C) for 10 minutes until a distinct reaction product was evident microscopically. The sections were then counterstained with Mayer's hematoxylin. Negative control sections were incubated without primary antibody.

Immunoreactivity of antibodies were graded according to the number of stained cells and the staining intensity in individual cells as follows: -, almost no positive cells; +, less than 50% of tumor cells showed weak immunoreactivity; ++, less than 50% of tumor cells showed strong immunoreactivity; +++, over 50% of tumor cells showed strong immunoreactivity. Grades - and + were regarded as weak expression and grades ++ and +++ were regarded as strong expression. Smooth muscle fibers which have strong immunoreactivity were used for internal controls of positive immunoreaction. Immunostaining was evaluated independently by three independent observers who were unaware of the clinical and histological diagnoses, and all of the sections were scored twice to confirm the reproducibility of the results. (Miskad UA, 2004, 2007).

Statistical Analyses.

The relationships between the results of the immunohistochemical study and clinicopathological variable were tested by chi-square test. $p < 0.05$ was regarded as statistically significant.

III. 3. DIAGRAM OF OPERATIONAL RESEARCH



CHAPTER IV
RESEARCH SCHEDULE

VI. 1 RESEARCH SCHEDULE

Month	May	June	July	August	Sept	Oct	Nov	Dec
Preparation	<u>X</u>							
Collecting Specimen		<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	
DNA extraction and Tissue Block Paraffin, Processing and Sectioning				<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>
Immunohistochemistry				<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	
Documentation	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>
Data analyses							<u>X</u>	<u>X</u>
Writing paper								<u>X</u>
Presentation Publication							<u>X</u>	<u>X</u>

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