INA RESPOND
INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

Newsletter March 2017

INA-RESPOND Secretariat

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In This Issue

INA102 (TRIPOD) Refresher Laboratory Training

The INA102 a.k.a TRIPOD is a tuberculosis study. The study protocol was ready in 2014, and the laboratory training for this study was first conducted on 9-10 October 2014. However, the network decided to postpone the study, and has just recently given a green light for it.

To make sure we have a good-quality study, our network decided to hold a refresher Laboratory training. The refresher training was conducted to brief the Laboratory Technicians regarding the changes in the study protocol, especially the ones related to additional specimens collection.

In addition, the aim of this refresher training is to provide coaching and technical uniformity in terms of specimen collection and processing until they are ready to be stored and sent to the reference laboratory. For more details on this training, read our TRIPOD study updates here.

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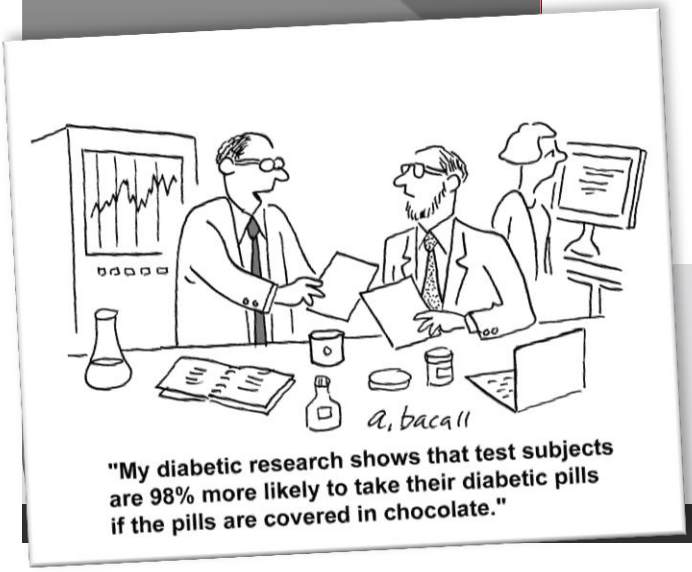


Evidence: Makes the Impossible Possible

As researchers, we are often interested in causal relationship of many diseases / other health conditions but often feel discouraged because proving causal relationship can be very difficult… or is it really? Read about it here!

Save The Date

Important Events & Meetings

9 March	NSC Meeting @NIHRD, Jakarta
28 March	*Hari Raya Nyepi* (Day of Silence) – religious holiday

March Birthday

11 Mar	Ms. Eni Yuani	NIHRD
28 Mar	dr. Tri Wibawa	INA101 Site PI Site 580

Announcement

We are going to hold our first 2017 Network Steering Committee Meeting (NSC) in March. The meeting will be held for one day on 9 March 2017 in *Ruang Ars Longa*, building 3, 3rd floor, NIHRD, Jakarta. For more information about this meeting, please contact the INA-RESPOND Secretariat. ☺

By:

dr. Herman Kosasih

AFIRE Study (INA101) Updates

As discussed during the PI meeting in January, 2017, our target is to disseminate our acute fever requiring hospitalization (AFIRE) results through several presentations and publications this year. To achieve this target, our laboratory team is currently very busy in testing the specimens from our subjects. This work is very complex as the specimens consist of buffy coat, plasma from three visits, respiratory and urinary specimens, and faeses; and the tests include molecular assay to detect the virus and bacterial genomes and serological assays to detect the antibodies from certain pathogens as indirect evidence of infections. Most of the tests that INA-RESPOND are conducting have never been applied in Indonesia. Therefore, we expect that there will be many new findings that are important for the health of the people that we can share with other scientists, clinicians, infectious disease specialists, clinical pathologists and microbiologists, epidemiologists, and health policy makers. The table below shows a number of pathogens that we are now searching for and the methods that we use.

Syndrome(s)	Pathogens	Methods
Systemic	Dengue virus	Molecular, Antigen and Antibody detection
	Salmonella sp, Rickettsia sp, Leptospira sp Chikungunya virus	Molecular, antibody detection
	Flavivirus	Molecular, assay
	Stapylococcus aureus, E coli, K pneumonia	Molecular assay
CNS	HHV-6	Molecular assay
	Toxoplasma	Antibody avidity
	CMV	Antibody avidity
Respiratory	Influenza A & B, RSV A & B	Molecular and antibody detection
	Adenovirus, bocavirus, Coronaviruses, enterovirus, HMP virus, parainfluenza 1-4, parechovirus, rhinovirus	Molecular assay
	B pertussis, B pseudomallei, C pneumoniae, C psittaci, H influenza, K pneumoniae, L pneumoniae, M catarrhalis, M pneumoniae, S aureus, S pneumoniae	Molecular assay
Gastro-intestional	Norovirus, enterovirus, Rotavirus, adenovirus, S typhi & paratyphi, shigella	Molecular assay
Genito-Urinary	E coli, Enterobacter aerogenes, enterococcus faecalis	Molecular assay

Thank you to all the site PIs, research assistants, and laboratory technicians, who have sent the specimens and data on time. It has been very helpful for us to keep our timeline. Please check the upcoming editions as we will update you three results regularly.

Detailed screening and enrollment progress is available in portal folder: Studies\INA101\Screening progress.pdf or go to the following link: https://ina-respond.net/EdmFile/getfile/797233

For further information about this study please go to: http://www.ina-respond.net/afire-study/

Latest News:
Former AFIRE Research Assistants (RA) Now Around The World

By:

dr. Anandika Pawitri

dr. Yan Mardian

(INA-RESPOND RA from Yogyakarta site: 1 May 2014 – 15 August 2015)

He was an RA for AFIRE study for about 1.5 years, and I can tell you he did a great job.

Can you guess where he is now? JAPAN! dr. Yan is currently a postgraduate student in Kobe University, Japan majoring in Hepatitis. Studying and doing research are his main activities there, but travelling has also become a part of him, somehow. If you decide to visit Japan, be sure to call him up, so he can take your around. His favorite season…? The Cherry Blossom, of course.

Working for INA-RESPOND as an RA has created a huge impact to dr Yan's academic activities in Japan. From processing and handling specimens the right way to ethical clearance administration, the research experience in INA-RESPOND has given him more confidence in performing his tasks.

dr. Mochammad Helmi Aziz

(INA-RESPOND RA from Surabaya site: 24 June 2014 – 19 August 2015)

Formerly an RA for INA-RESPOND AFIRE study, dr. Helmi is known for his accuracy in completing the study documents.

dr. Helmi is a Research Master Student of Infection and Immunity in Erasmus MC, Rotterdam, Netherland. So, what made him go 11,883 km from his hometown? His thirst for acquiring new knowledge in research and medical field, for one, and as Ralph Waldo Emerson said, "It is about pushing your limits and venturing beyond your comfort zone".

Dr Helmi is focusing on Infection and Immunology because that is his passion. Working in INA-RESPOND has opened up his opportunities to embrace his passion. Professor Usman Hadi (AFIRE PI in Surabaya site) inspires and fully supports him in science enrichment and conducting good clinical research.

Although studying abroad sounds like an all-time-fun, dr Helmi knows firsthand that conducting research is not easy at all. He has had his ups and downs in the learning process. A little giveaway… lack of sleep is to be expected! ☺

dr. Annisa (2nd from the right)

Dr Annisa Tridamayanti

(INA-RESPOND RA from Yogyakarta site: 20 March 2015 – 9 August 2016)

Working together with dr Gandhi, dr. Annisa was a perfect work partner. She is a very observant and decisive RA. Currently, she is a junior resident in Cardiology Department in *Universitas Sebelas Maret*, Surakarta, Central Java.

Just like the others, chaotic and exhausting situations have become her everyday meal. However, in the midst of her busy activities as a

resident, she sometimes experiences "funny" things:

"Here, I'm studying anatomy, physiology of heart, and other educational related stuff. However, as a junior resident, I am also expected to do other casual stuff such as administration, department household and sometimes as weird as returning my senior's wrong-sized bikini. Yes, you read that clearly," she wrote, "I am a small-medium sized woman who wears hijab. Can you imagine the awkward look on the bikini seller's face when I asked her if I could change the size to XXL?"

She remembered feeling really happy working as an RA. There were no extreme pressure, no frantic environment, no piles of reports. For her, working in INA-RESPOND has helped her going through the residency. She learnt a lot about research methods, and many of her seniors asked for her help to explain about the matter.

Dr Gandhi Anandika Febryanto

(INA-RESPOND RA from Yogyakarta site: 20 March 2015 – 9 August 2016)

Dr Gandhi was an RA for INA-RESPOND sepsis study.

Honestly, he is the TALLEST RA that I've ever met. He's almost as tall as a mini mango tree; he's 186 cm! That's tall for Indonesian standard. Here is his letter from London!

London, 21 February 2017

Good day everyone!

How are you doing? I hope you are all in good condition and high spirited. I'm doing really well here, in London. Right now I'm taking Master Clinical Ophthalmology program in University College London. It's a 1-year program starting from September 2016 until September 2017. So, I'm half way there ☺

What I love about studying abroad, compared to studying in my home country, is the closeness between students and teachers. Here, students and teachers are like friends, and we respect each other. The communication between the two is well-established, making the learning process and environment more conducive. In addition, the facilities are really good; they have an integrated electronic library, so students can look for any literature without much difficulty.

As much as I love it here, unfortunately, there is no NASI PADANG (yes, for me it's a "serious" problem). Buying meals at restaurants is really expensive here, so I significantly improve my cooking skill in order to save some money. I love watching films but here I have to think twice before going to the cinema. It's quite expensive, and they don't have Indonesian subtitles. Do I miss my family? Sure do! Luckily, we have video call now.

My two-year experiences in INA-RESPOND have taught me a lot. I learnt about teamwork, how to overcome language boundaries and interact with foreign experts, and how to present your research. The most important thing was the opportunities to meet and know great researchers motivate me to chase my dream abroad. From them I've learnt that I have to break new ground and broaden my knowledge.

Hopefully, in the upcoming years all of us will achieve success and prosperity; and will keep on rockin' the world of science.

With regards,

Gandhi

Dr Patricia Tauran, SpPK

(INA-RESPOND RA from Makassar site: 4 September 2013 – 9 February 2015)

She is one of the early RAs who worked for AFIRE INA-RESPOND study. We recruited dr. Patricia when she was a Clinical Pathology resident at *Universitas Hasanuddin*, *Makassar*, South Sulawesi. After graduated, she works as a Clinical Pathologist at *Lakipadada, Tana Toraja*, around 7.5 hours from Makassar; and a part-time Clinical Pathology and Clinical Data Consultant for INA-RESPOND.

As a consultant in INA-RESPOND, Dr Herman makes her read a lot scientific journal to keep her knowledge up-to-date. Dr Pat is also learning and observing laboratories in all INA-RESPOND sites, and the information gathered is used as reference to make constructive suggestion for the improvement of the hospital lab where she work is working now.

INA-RESPOND has opened up her network; it introduces her to a lot of experts from Indonesia and other countries. In fact, from her meeting with one of the supervisors from Thailand through INA-RESPOND, dr Patricia can publish her manuscript on The American Journal of Tropical Medicine and Hygiene (AJTMH). You think that's cool? Wait until you "hear" this… She is using her RA salary to build a small lab! Her dream is to build a bigger infectious lab. Amazing, isn't it? Good luck, dr. Patricia!

Dr Indri Hapsari

(INA-RESPOND RA from Semarang site: 8 July 2013 – 2 July 2016)

dr Indri was with the INA-RESPOND AFIRE study team for quite some time. She's also one of our most reliable RAs. Where is she now? She's writing us from The Netherlands!

Hi everyone!

I'm so excited to get an email from the INA-RESPOND Secretariat. Honestly, I miss the routine I did as an RA, and most importantly, I miss the Secretariat personnel!

I'm doing great here. I'm taking Microbiology Master Program in Radboud University Nijmegen, Netherland. This is a completely new journey for me and my family (I'm taking my husband and daughter). Having my family here makes me feel secure and comfortable.

As for my academic life, I have to make a lot of efforts to stay ahead as it has been quite a while since the last time I was in school, but guess what... I've got the highest score for my last compulsory course (host-microbe interaction/immunology)!

Right now I'm undertaking an internship in the Laboratory of Pediatric Infectious Disease, Radboud University Medical Center; working on *Streptococcus pneumoniae*. I feel like I'm the PI, the RA, the Lab Technician, and also the Data Manager all at once! ☺

My experiences as an RA in INA-RESPOND study have helped me a lot in conducting my research. I have become familiar with organizing sample, collecting data, and doing administrative stuff. In addition, working with people from various backgrounds is no longer an issue for me. Of course, there is a different academic culture between here and in Indonesia. I don't feel too much hierarchy and have more egalitarian. I'm working in a lab, doing the 'dirty job' as well as being a PI who has to fully understand why I did this and that. Definitely I'm supervised all the time.

I hope I can continue my studies and get my PhD in the near future, and perhaps, collaborate with INA-RESPOND someday! See you soon!

Study Updates:

INA102 (TRIPOD) Refresher

By:
dr. Nurhayati

The INA102 Refresher Laboratory Training was conducted on 17-18 February 2017 at RSU Tangerang, Tangerang. The training was held specifically for Laboratory Technicians (LT) of INA102 study (TRIPOD). The aim of this refresher training is to provide coaching and technical uniformity in terms of specimen collection and processing until they are ready to be stored and sent to the reference lab.

The two-day training was attended by Ni Nyoman Eriyanti (Sanglah Hospital, Denpasar); Tri Kusuma Wadhani and Anjis Pribadi (Dr Kariadi, Semarang); Catur Endra Kurnia Ackri and Ayu Rizki Emilia (dr Soetomo, Surabaya); Dwi Sri Winarti, Linda Oktabriana, and Libertha Clara Manintan (dr Sardjito, Yogjakarta).

The refresher training was given by dr. Dewi Lokida, Sp.PK (INA-RESPOND Laboratory Consultant - RSU Tangerang District), Ms. Evi Herawati (Banten Phlebotomy Assessor Team - RSU Tangerang), Ms. Deni Pepy Butarbutar, Ms. Gustiani, Mr. Ungke Anton Jaya, Ms. Wahyo Nawang Wulan, and Ms. Rizky Amalia Sari.

Training began with a review of the Universal Precaution. In this session, participants were reminded about self-protection procedures and how to use the personal protection equipment. Since the LTs will be dealing with many infectious/contagious materials, it is important that they know how to protect themselves so they won't be infected.

Next came the pre-analytical preparation; this is the stage where participants learn how to prepare the equipment needed for specimen collection, ensure the right specimens are collected, giving specimen's number label and subject identification number. This stage is also very important to ensure that the specimens taken, the label, and subject identification number are all in accordance with the study protocol.

The next training session was more directed to research protocols i.e. blood-taking training (phlebotomy) using closed system technique, isolating isolate into micro bank tube, PBMC cell isolation, and aliquoting other specimens. For phlebotomy training, participants were given fake arms to practice on as many times as they want. After mastering the phlebotomy techniques, the participants practiced by taking other participants' blood directly.

After specimen preparation was completed, the next session covered specimen storage procedures, research form completion, and specimen data entry to the repository database.

At the last session participants were given information about the specimen shipping and handling procedure.

All training materials were given to representatives of each.

It is expected that after the training, participants can share the information to their co-workers at site and develop their knowledge.

REPORT:

CROI 2017 and INA-PROACTIVE

By:
dr. Dona Arlinda

Fig1: From left to right: dr. Dona Arlinda (NIHRD, Jkt), Dr. Rudi Wisaksana (RS Hasan Sadikin, Bdg), Dr. Evy Yunihastuti (RSCM, Jkt)

INTENSE is the one word that can describe the Conference on Retroviruses and Opportunistic Infections (CROI), held on 13-16 February 2017 in Seattle, Washington, USA. Dr. Rudi Wisaksana (Hasan Sadikin Hospital, Bandung), Dr. Evy Yunihastuti (Cipto Mangunkusumo Hospital, Jakarta), and myself were the three delegates from Indonesia attending the conference (Fig. 1).

CROI is a scientific forum to exchange the latest research findings on HIV/AIDS and its complications, as well as selected other emerging infections. This annual meeting brings together up to 4000 researchers and leaders in the field of HIV/AIDS from all over the world. The goal is to facilitate translation of laboratory and clinical research findings into actionable strategies to fight the HIV pandemics.

This year, CROI accepted over 1,000 abstracts covering the topics from basic molecular virology to implementation researches, HIV prevention, diagnostics, and the latest therapeutics development, clinical pharmacology, HIV cure, antibodies and reservoirs, HIV complications, HIV cost modelling, and Zika virus as the selected topic for emerging infection.

Interestingly, 56.5% of those abstracts originated from the America, 22.5% from Europe, while only 14% from Africa and 7% from Asia and Australia.

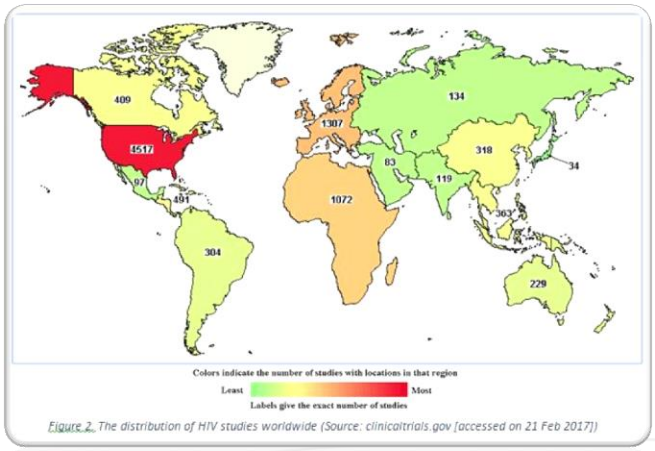


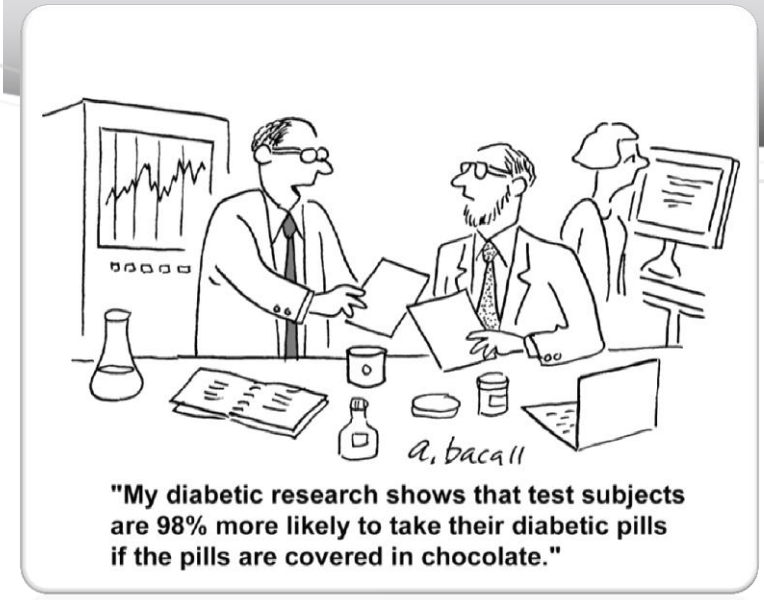
Figure 2. The distribution of HIV studies worldwide (Source: clinicaltrials.gov [accessed on 21 Feb 2017])

Knowing that in 2015, Africa and Asia Pacific were the top 2 regions with the highest number of people living with HIV (30.6 million in Africa and 5.1 million in Asia Pacific), that distribution seemed awfully imbalanced. HIV is by far the most extensively studied virus, so are we not having enough HIV studies in Africa and Asia Pacific? Probably so, the distribution of HIV studies worldwide from clinicaltrials.gov showed that Africa and Asia Pacific are lagging behind the Americas (Fig. 2). Then there is also the question whether we don't have enough (internationally acknowledged) publications of the available studies. That is something that we must address on the upcoming Prospective Observational Cohort Study of HIV Infection and Risk Related Coinfections/ Comorbidities in Indonesia (INA-PROACTIVE) i.e. the HIV study in INA-RESPOND network.

The three of us would like to thank Dr. M. Karyana for his endless encouragement and INA-RESPOND Secretariat for their dedication and support. We look forward to five years (or more) of INA-PROACTIVE and hopefully, another experience in CROI as oral speakers presenting fascinating findings from INA-PROACTIVE.

A Piece of Evidence: Makes The Impossible Possible

By:
dr. Aly Diana



What comes to your mind when you read the text below the comic? After hearing the reported results, will you recommend using diabetic pills covered in chocolate to improve compliance? Some may say yes; why not?! Some may say it depends. Some may say, NO; it must be a mean joke giving chocolate to diabetic patients!

Surprisingly, a cross-sectional study looking for cardiovascular risk factors in Luxembourg, involving a random sample of 1,153 adults, found that daily chocolate consumption is inversely associated with insulin resistance. I will not focus on how robust the study and whether it passes the critical appraisal checklists or not. Rather, I want to highlight that something that sounds like a joke can actually be transferred into a real scientific article and be published in a credible journal.

As researchers, we are mostly interested in causal relationship of many diseases and other health conditions but often feel discouraged because we think that proving causal relationship can be very difficult. Basically, there is no strict formula/ algorithm to assess whether a causal inference is appropriate or not. However, there are some rules and guidance (as listed in "Reference Manual on Scientific Evidence", p. 597-606) that we should try to follow (should exist) to establish causality; they are: 1) temporal relationship, 2) strength of the association, 3) dose–response relationship, 4) replication of the findings, 5) biological plausibility (coherence with existing knowledge), 6) consideration of alternative explanations, 7) cessation of exposure, 8) specificity of the association, and 9) consistency with other knowledge.

Surprisingly (again), the absence or existence of one or more factors above does not ensure the true causal relationship. Drawing causal inferences is more of an art, which requires searching analysis, judgment, and interpretation; based on biological plausibility, of why a factor or factors may be absent despite a causal relationship, and vice versa. At this point, the expertise of researchers plays a big role in explaining causal relationship in our study - to some extend it is more of a subjective point of views and perspectives than objective processes.

Closing remarks:

Science is a combination of facts and arts. So far, we may justify causality based only on our mere knowledge. Let's forget that there are so many unanswered questions, unfolded mysteries, and unclear mechanisms in this world (and that's why researchers are needed). The point is it is totally okay to mention that the mechanism is unexplained/ unknown or the reason is uncertain; and acknowledge that more studies are required to close the gaps. It's about collecting pieces of evidence to complete a complex puzzle.

These are some strong statements to encourage us in doing a study and writing an article to find/explore causality:

- The absence of an exposure-response relationship does not exclude a causal relationship.
- A lack of mechanistic data, however, is not a reason to reject causality.
- The absence of other lines of evidence that support a cause-and-effect interpretation of the association, however, is not a reason to reject causality.

Statins for All Infectious Diseases?

TB Bacteria Behavior That May Cause Them to Slip Phagocytosis Process

By:
Ms. Maria Intan Josi

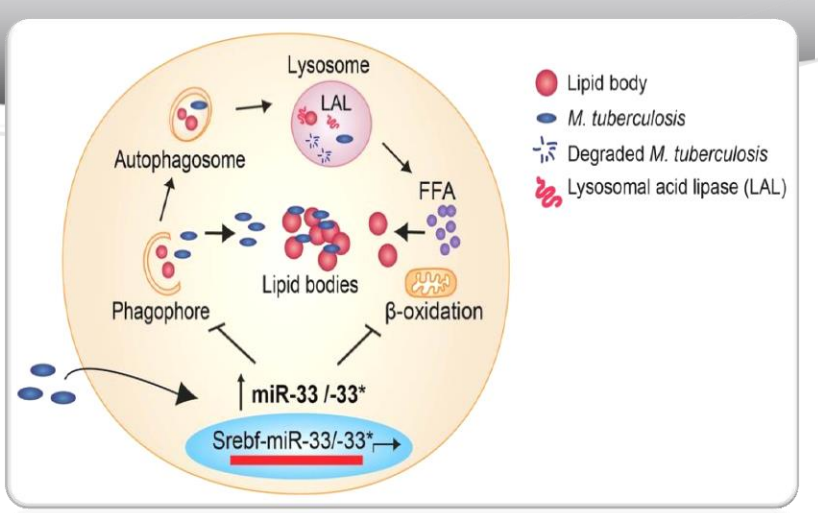


Fig.1 - Phagocytosis Flow in M. Tuberculosis bacteria

The use of statins in reducing the risk of infections and their related complications has been around since 2000. From the studies conducted so far, researchers have found out that statins are capable of inhibiting the enzyme, *3-hydroxy-3-methylglutaryl coenzyme A (HMG COA) reductase*. *The* HMG CoA enzyme controls the formation of cholesterol in mevalonate pathway. Therefore, statins have been developed as an agent that makes HMG CoA as the target to reduce cholesterol levels in plasma and have been extensively studied in relation to atherosclerosis.

In addition, statins do not only lower cholesterol level but also decrease the level of intermediate products in cholesterol synthesis such as *farnesylpyrophosphate & geranylgeranylpyrophosphate*, which play a crucial role in some intracellular signaling pathways.

It seems that this effect is the main explanation for the *pleiotropic effects* of statins, namely increasing the functions of endothelial cells, reducing the effects of inflammatory, and reducing the formation of *thrombus*, which include anti-inflammatory effects.

Statins also play a part in counteracting the damaging effect of sepsis by inhibiting expression and reducing the fragments level of prothrombin as well as increasing the expression of thrombomodulin. In addition, statins have been shown to have direct effects in inhibiting the development of microorganism. In fact, some types of statins have been proven to be able to prevent sepsis (for example, atorvastatins and pravastatins).

Because statins have a function in regulating lipid, affect the immune system, and can even prevent sepsis, statins are widely used as an additional medication in various diseases caused by viruses/ bacteria such as influenza, hantavirus, hepatitis C, HIV, and tuberculosis (TB). Moreover, there is a study combining the use of statins with angiotensin receptor blockers to treat Ebola virus.

In addition to the use of statins as additional treatment for many infectious diseases, can statins be used as an additional therapy in TB infection? A research in 2016 shows the uniqueness of tuberculosis bacteria capable of hiding and taking the food of macrophages in the phagosytosis mechanism.

In the phagosytosis mechanism, foreign cell will be inserted into cells, and then made lysis by lysosomes. While entering macrophages, most bacteria will be wrapped in vesicles (sac) called phagosome. These vesicles then merge with lysosomes. Lysosomes are spherical vesicles that contain enzymes and chemicals capable of destroying bacteria.

Recently published study describes how tuberculosis bacteria react to mammals' macrophages cell. Tuberculosis bacteria create a piece of genetic material, which in a higher level, called microrna-33 (miRNA-33); this genetic material is able to stop the ability of macrophages in digesting and destroying tuberculosis bacteria. However, at the same time, this

genetic change causes the cells to build fat for tuberculosis bacteria as their food source. In other words, this genetic change is beneficial to TB bacteria as it makes them last longer in the cells.

Although this study was performed on rats, the same mechanism was also found in human cells infected by TB bacteria.

TB bacteria can avoid lysosomes' traps, so they can roam freely at the cytosol cells (liquid inside cells). However, the cytosol has a back-up mechanism called autophagy, in which tuberculosis bacteria are re-searched to be brought to lysosomes; this process occurs repeatedly (Fig. 1).

In addition, tuberculosis bacteria can also take advantage of the phagosytosis mechanism called autophagy. In autophagy, aging cells will be wrapped, destroyed, and recycled. Autophagy also has a mechanism to control the level of fat and serves as a back-up system in eliminating dangerous bacteria.

Specifically, the study found that the tuberculosis bacteria's protein was able to trigger immune system signal in macrophages called NFKappaB protein, which triggers genes to produce more microRNA-33. This dramatically blocks the signal sent out by several autophagy genes, and in return keeps the fat level low.

The use of statins in TB treatment was proposed considering that tuberculosis needs fat to survive.

The question is then, "Is it possible that statins as cholesterol synthesis inhibitors are able to hold the formation of fat in macrophages?"

This issue was answered by a research in 2010 where the study stated that miRNA-33 must be ciphered by the same genes at the time when statins occur. In other words, statins actually cause macrophages to form more miRNA-33 even when the cholesterol level is low.

After learning the role of miRNA-33 and the formation of fat in tuberculosis infection, the study author argued that statins should not be used as an additional therapy. Instead, we should choose other more appropriate agents such as antisense oligonukleotida.

The formation of lipid could be countered by using antisense oligonukleotida, which is a molecular chain set in the right size which is able to capture the Mir-33 and block its action. This action is similar to the treatment using mipomersen, an antisense molecule available for the treatment of derivative diseases causing high level cholesterol.

So…, can statins be used to treat all kinds of infections?

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INA-RESPOND Newsletter

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We would like to hear from you. Go ahead and send us your scientific articles, team profile, or feedback to INA.Secretariat@ina-respond.net