INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

July 2018

INDONESIA DELEGATION VISIT TO US-NIH

Requesting Study Data FOR PUBLICATION PURPOSES

The Art of Using Wikipedia for Research

Teixobactin and Odilorhabdins: A New Hope in Antimicrobial Resistance Era

NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2018

INA-RESPOND Steering Committee Meeting

8-9 August 2018

The Hermitage Hotel,

A Tribute Portfolio Hotel,

Jakarta

INA-RESPOND newsletter

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FEATURES

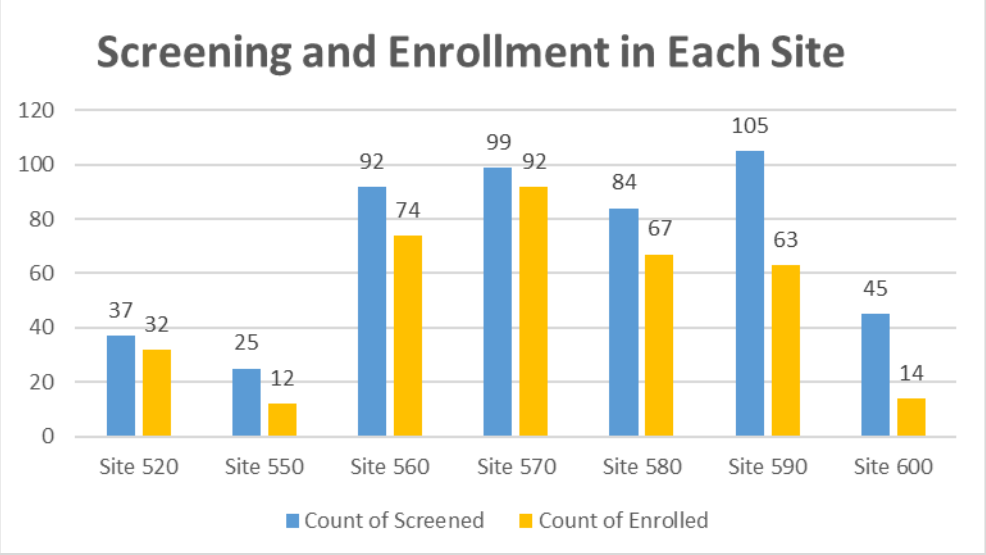
INA-RESPOND Newsletter

TRIPOD & INA-PROACTIVE Study Updates

By: ANANDIKA PAWITRI, CALEB L. HALIM, LOIS E. BANG, M. IKHSAN JUFRI, VENTY MULIANA SARI

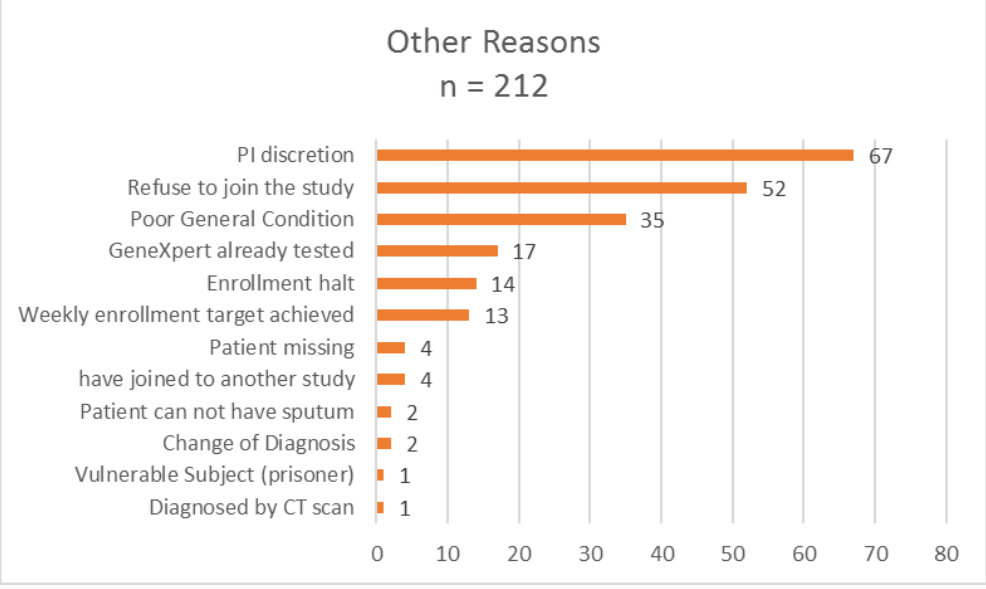
INA102 Screening and Enrolment

By 16 July 2018, sites had enrolled 354 subjects. Sites enrolled 72.6% of screened patients (487 screened patients). Total subjects enrolled based on our enrolment target is 57% (354 from 660). Enrolment progress until 16 July 2018 can be seen in the graphic on the right.



Reasons for "Other" Reason

There are many reasons why potential subjects cannot be in our study. If the reasons are not included in the inclusion or exclusion criteria, we will put them in 'other' category. On the right is the information:



Sites updates

Site 510 (Hasan Sadikin Hospital, Bandung) will join us in TRIPOD study in the near future. The complete site team members will be announced soon. Meanwhile, the Secretariat is preparing for the Site Preparation Visit.

Site 600 has joined the study. Dr Hendra Gani Harahap as a new Research Assistant will accompany dr Dashari in the study.

INA104

HIV study has been active for six months, and up to 23 July a total of 326 subjects has been enrolled (311 adult and 15 pediatrics subjects). Sites enrolled 70% of screened patients (468 screened patients). Enrolment failure reason is mostly because the patients were represented by their family members when they came to the clinic (not by themselves). Two new sites, Ansari Saleh Hospital and Persahabatan Hospital, each enrolled one subject last week.

No new additional site signed contract this month. Currently, our legal officer is working on extending the contract with all 12 sites since all contracts expired on 15 June.

This week (23 – 26 July) we are conducting Site Preparation Visit to Site 660 (Wahab Sjahranie Hospital) in Samarinda. Site 640 (St. Carolus Hospital) and Site 650 (Budi Kemuliaan Batam Hospital) are working on the final preparations for site activation. Hopefully, within two weeks these two sites will join the study. Site 580 has been granted Local Ethical Committee approval for HIV Study and is now waiting for final document of permission to be signed by the Hospital Director. Unfortunately, we have not received news from site 670 regarding the contract with INA-RESPOND.

The aim of INA-RESPOND is to build quality research network in Indonesia. That also means we have to spread our wings from far west to the far east of Indonesia. Now with the HIV study, we have collaborated with hospitals in Papua island located in the far east of Indonesia. Next month we will conduct Site Assessment Visit to three cities in Papua; Sorong, Jayapura, and Merauke. As for the far west part of Indonesia, we have send Collaboration letter with Zainoel Abidin Hospital, Aceh and are still waiting for their favourable reply.

Per 23 July, INA-PROACTIVE is implementing protocol Version 2.0. All sites that already have PIMA Analyzer may proceed according to the latest protocol version. However, sites that do not have the PIMA Analyzer will have to hold the testing until Secretariat send them one. Regardless, all active sites will use SDW and CRF Version 2.0.

Site	Activation	Enrolled Subjects	Site	Activation	Enrolled Subjects
Site 610 (Tangerang Hospital)	09 Jan 2018	70	Site 570 (Soetomo Hospital)	26 Apr 2018	24
Site 600 (Adam Malik Hospital)	12 Mar 2018	50	Site 630 (Ansari Saleh Hospital)	10 Jul 2018	1
Site 550 (Wahidin Hospital)	13 Mar 2018	53	Site 590 (Sardjito Hospital)	18 Jul 2018	1
Site 530 (Cipto Mangunkusumo Hospital)	3 May 2018	22			

INA-RESPOND Newsletter

INDONESIA DELEGATION VISIT TO THE US-NIH

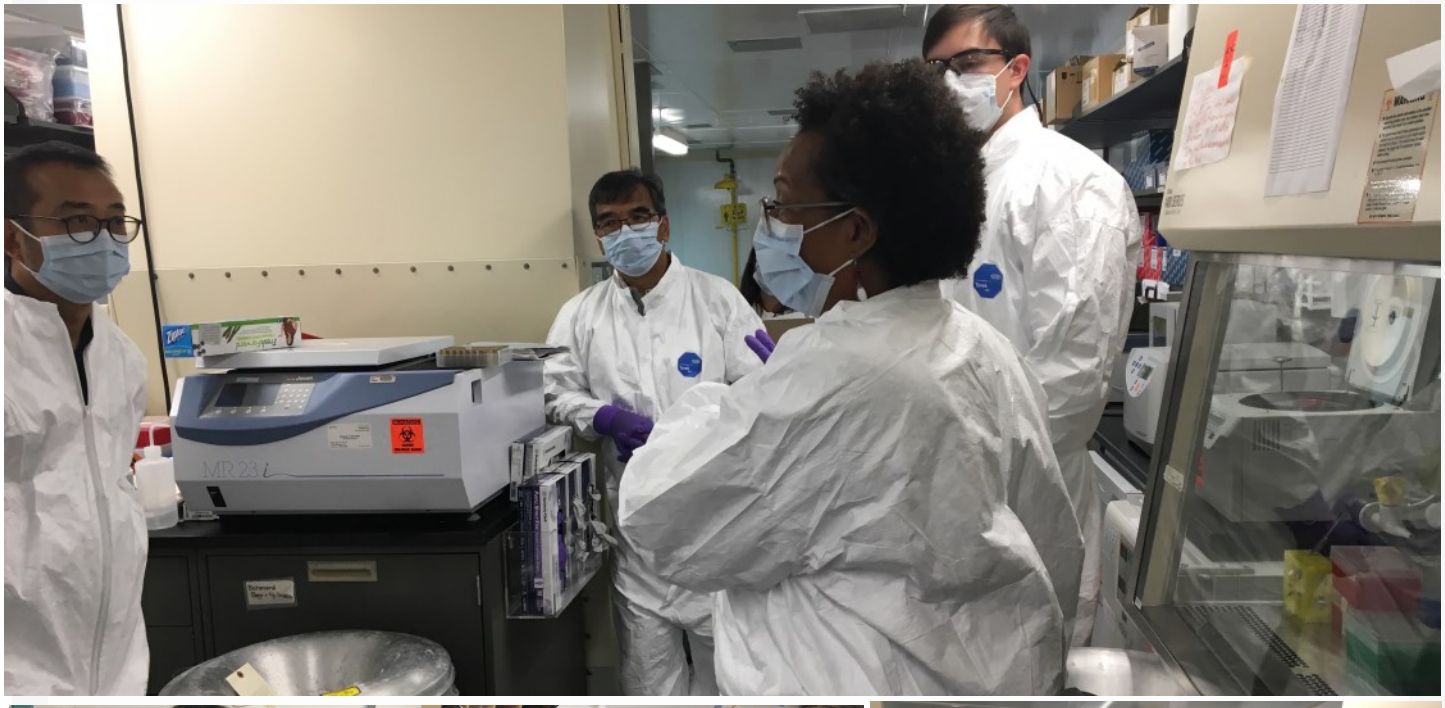
By: HERMAN KOSASIH, M. KARYANA

REPORT

RePORT and CFAR Collaboration Meeting

A collaborative meeting of RePORT (Regional Prospective Observational Research in Tuberculosis) and CFAR (Center for AIDS Research) was conducted on 2-3 July 2008. The purpose of this meeting was to understand the resources and gaps in US-NIH funded Tuberculosis (TB) research. TB researchers from all countries under RePORT consortia were invited, along with the CFAR investigators who have expressed an interest in the potential of this proposed collaboration and in the portfolio of Tuberculosis Research. During this productive meeting, current research portfolios were shared, including research on the epidemiology of TB, biomarkers in TB prevention, diagnosis and prognosis, TB pathogenesis, TB diagnostics, TB treatment response and mortality, TB/HIV in pediatrics, and TB HIV diabetes trisection. At the end of the meeting, future research areas of interest were shared and partnerships for future cross-consortia collaborations to enhance synergy and advance TB/HIV research were discussed.


Danke
Thank you
Merci
Gracias
Takk
Dziękujemy



INDONESIAN DELEGATION VISIT TO THE US-NIH

The Indonesian delegation was led by Dr. dr. Irmansyah, SpKJ. Other members were Dr. drg. Tati Suryati as the head of scientific review board, NIHRD; dr Muhammad Karyana, MKes as the chair of INA-RESPOND Steering Committee; and dr Herman Kosasih from INA-RESPOND scientific division. The objectives of the visit that was conducted from 11-13 July 2018 were to obtain information about the NIH structure and its clinical research facilities, funding and training available, and to discuss research opportunities.

On the first day, Dr Chuen-Yen Lau introduced all the integrative facilities of the clinical center, followed by a meeting with the National Center for Complementary and Integrative Health (NCCIH) to discuss current research conducted by NIHRD and NCCIH and the possibility of future collaboration. Later in the afternoon, the delegation had a chance to attend how protocols, including the schistosomiasis study, were reviewed by NIAID scientific reviewed board. In late afternoon, Dr Irmansyah had the opportunity to discussed and shared ideas with the team from the National Institute of Mental Health (NIMH).

On the second day, US-NIAID prepared a one-day tour to Frederick area, one-hour drive from NIH main campus, to visit laboratory facilities. The first place was the biorepository laboratory where Dr Marcia Lara explained in details the requirements of the specimens to be stored in this facility, the procedures when specimens are received, stored in hundreds of freezers, liquid nitrogen tanks, and walk-in freezers with different temperatures, and shipped. In the afternoon the delegation visited For Detrick, the US Army Campus where both NIAID HIV laboratory and Integrated Research Facilities (IRF) are located. In the HIV lab, Robin and Helena shared their experience regarding HIV assays in their lab, and offered to assist INA-RESPOND reference lab to achieve the same standard. At the end of the day, the delegation visited IRF, which is part of the National Interagency Biodefense Campus, a group of federal biomedical research facilities. Here the delegation was escorted by Michael Holbrook, the chief of containment supervisor, and were fascinated by the advanced imaging technology and other state-of-the-art features inside this secure laboratory.

On the third day, Dr Clifford Lane, the deputy of US-NIAID, head of Clinical Center and our INA-RESPOND governing board member, accepted the delegation. During the one and half hour meeting, Dr Lane explained the structure of US-NIH and NIAID in more details. The discussion was very fruitful and boosted the motivation to enhance the collaboration between the two institutions Dr Lane also emphasized the need for the extension of the implementation agreement between US-NIH and Indonesia NIHRD. Before noon, the delegation was impressed by how the US-NIH Library of Medicine was designed to protect all the manuscripts from threats and by their collections from all over the world. At the end of the visit, the delegation visited the HIV clinic, and had a very valuable discussion with DIAIDS and RePORT team regarding our TRI-POD and Pro-Active studies. At the end of the trip, Sophia prepare a dinner party to welcome and introduce the delegation to all the team Division of Clinical Research (DCR). Thank you very much to all the DCR team for your hospitality during our stay.

INA-RESPOND Newsletter

Requesting Study Data for Publication

By: M. HELMI AZIZ, M. MILA ERASTUTI, and NURHAYATI

Since INA-RESPOND was established, the network has had several studies. Some of these studies are on-going, but a couple of them (AFIRE and Sepsis) have completed their enrollment. Like any other study, these studies have valuable data/information. Have you ever wondered how you can access the data to process it into a publication?

This article will summarize our new Standard Operating Procedure (SOP) called "Study Data Usage for Publication" and inform you how to obtain our study data for publication. There are four parties involved in this new SOP:

Manuscript Writing Committee (MWC)

The MWC consists of up to 5 members. They may be the study's protocol Principal Investigator (PI), protocol Co-PI, investigators, study team members, Steering Committee (SC) members, and designated INA-RESPOND secretariat staff and/or study statistician (if applicable). In addition, researchers outside of the study team or network are welcome if the SC member from the involved site granted their approval. MWC appoints one leader (LMWC) who will be the primary contact during the study data request process. MWC is responsible for the development of concept plan, data analysis, writing the first draft of publication, and publication.

Approval Committee (AC)

The AC is responsible for providing review, decision, reassignment, and withdrawal of the submitted concept plan.

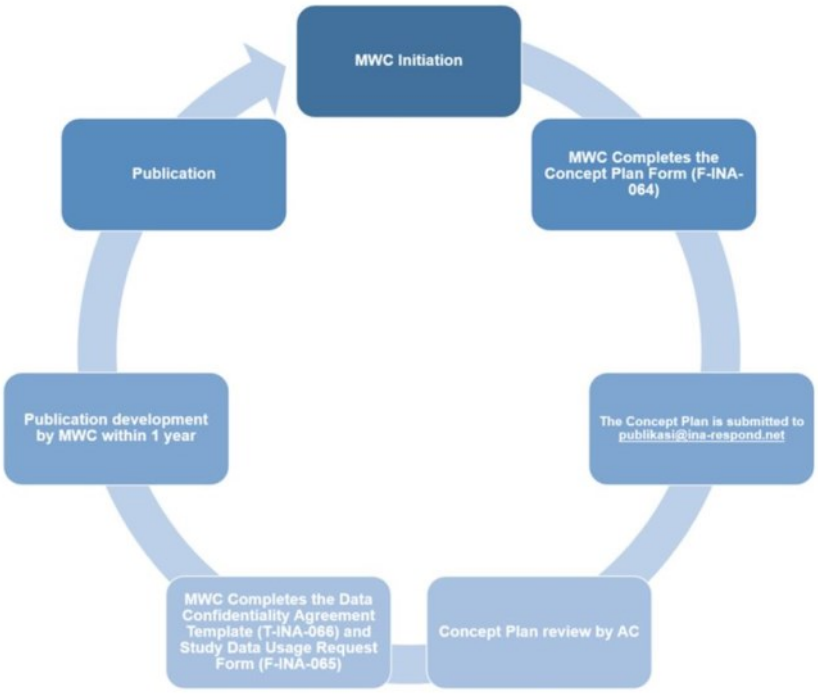


Figure1. Flow chart of request and approval procedure of INA-RESPOND study data.

Data Manager (DM)

The DM will provide the requested data by MWC after AC approves the study data request.

Publication Specialist (PS)

The PS is responsible for coordinating the procedure of study data request until the publication. PS will bridge the communication between MWC, AC, and DM related to study data usage for publication.

The procedure that needs to be followed to obtain the desired study data can be seen in Figure1 above.

The Investigator and/or study team within the INA-RESPOND network and/or designated INA-RESPOND secretariat staff initiate the formation of MWC (max 5 members) and appoint one leader of MWC (LMWC).

MWC develops the idea to use study data for publication by completing the INA-RESPOND Concept Plan (CP) and Approval Committee's (AC) Decision Form (F-INA-064).

The F-INA-064 form is submitted to PS via publikasi@ina-respond.net for further review by the AC. The MWC will get the final decision from PS within 10 working days after submission.

If the F-INA-064 form is approved by AC, MWC must complete the Data Confidentiality Agreement Template (T-INA-066) and Study Data Usage Request Form (F-INA-065) and submit the forms to publikasi@ina-respond.net for further review by DM team. If the F-INA-064 form is approved with minor revision or rejected, the MWC needs to provide revision according to the AC's comments and repeat the steps or submit new request for study data usage. DM team will send the requested study data within 10 working days.

After the MWC received the requested study data, the MWC will be responsible for data analysis and publication development within one year after the approval is received. LMWC should ensure the final draft of publication is submitted for approval to the authors and those whose acknowledge prior to the submission to the journal etc.

The MWC must update the publication progress to the AC through the Publication Specialist (PS) designee every 3 months by email to publikasi@ina-respond.net.

If MWC fails to produce publication within one year of approval, AC will notify the MWC for reassignment or withdrawal.

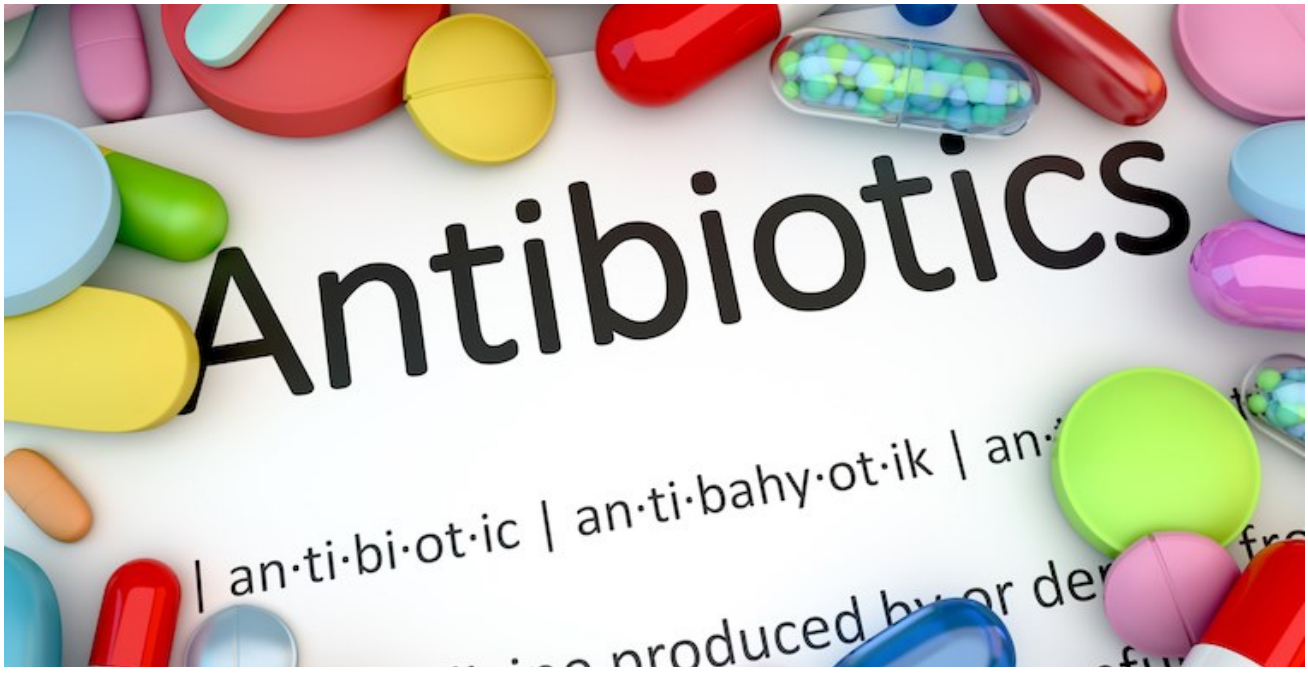
We also developed the Study Data Usage for Publication – Site Guidance to be used by INA-RESPOND network site and the document will be distributed within this month. INA-RESPOND Clinical Research Site Specialist and Clinical Research Associate will provide training for this topic either by Teleconference and/or on-site during site monitoring visits.

All the forms that are required to be completed can be found in INA-RESPOND portal or INA-RESPOND website (https://ina-respond.net/downloads-links/). If you have an idea but still do not know where to start you can contact us at publikasi@ina-respond.net for further guidance.

INA-RESPOND Newsletter

Teixobactin and Odilorhabdins: A New Hope in Antimicrobial Resistance Era

By: M.HELMI AZIZ



Antibiotics are among the most frequently prescribed medications in modern medicine. The first antibiotic, Penicillin, was discovered by Alexander Flemming in 1928, and since then, more than a hundred compounds from different classes of antibiotics have been introduced for medical purposes. By 2050, it is predicted that antimicrobial resistance (AMR) will be responsible for more deaths than cancer. The latest class of antibiotic was found in 1987, and despite the rise of AMR, no new class has been discovered since. due to lack of pharmaceutical company investment interest. This month article summarizes two breakthrough candidates of antibiotic classes, Teixobactin and Odilorhabdins.

Teixobactin

In 2015, Ling *et al.* published a paper in Nature journal about a new class antibiotic called Teixobactin [1, 2].

Teixobactin is produced by a species of β-proteobacteria, *Eleftheria terrae*, genus *Aquabacteria*. Ling *et al.* isolate this new compound using iChip technology (Figure1) which is primarily used to cultivate the "uncultivable" microorganism [1, 3]. The extract from iChip cultivation of *E. terrae* attracts attention since it is inhibiting the growth of *Staphylococcus aureus* (*S. aureus*) [1, 3, 4]. Later, using mass spectrometry, amino acid analysis, and NMR-spectroscopy, the extract structure was elucidated, which lead to the discovery of Teixobactin [3].

The relatively high molecular mass (1242 g mol^{-1}) of Teixobactin correlated with its function as antibacterial properties [3]. Teixobactin blocked lipid II (peptidoglycan) and lipid III (teichoic acid) – the biosynthetic precursor of the bacterial cell wall based on molecule-molecule interaction [3]. Although Teixobactin has the same mechanism as vancomycin, which also lipid II binder, it does not show cross-resistance

with Vancomycin [3]. Moreover, the in vitro direct comparison between those two antibiotics showed that Teixobactin has a faster killing profile of *S. aureus* [3]. However, lipid II and lipid III are abundantly found in Gram-positive bacteria, but not in Gram-negative bacteria. This suggests that Teixobactin has little efficacy or ineffective to the Gram-negative bacteria, which have different cell wall structure [2, 4].

Related to toxicity, in vitro studies reveal that Teixobactin showed no adverse effects by showing the absence of cytotoxicity, hemolysis, and genotoxicity [3]. A good half-life in plasma of Teixobactin also has been observed in rodents, dogs, and humans [3]. Later, two studies using a mouse-MRSA-sepsis and *Streptococcus pneumonia* lung infection models proved that Teixobactin has comparable efficacy with Vancomycin and Amoxicillin respectively [3].

Scientists had tried to generate Teixobactin-resistant mutants' Gram-positive bacteria but they failed. Resistance to Teixobactin is less likely to develop since it is targeting lipid molecules, not a protein that is encoded by a gene that could mutate and develop resistance. However, Teixobactin is produced in natural environment, meaning there are microbes around the environment that are naturally resistant to Teixobactin. These microbes can transfer the resistance genes to the pathogenic bacteria which similar to the history of Extended-spectrum beta-lactamases (ESBLs) resistant genes transfer from environmental microbes [2].

Odilorhabdins

A new broad-spectrum antibiotic was recently discovered and published by Lucile *et al.* earlier this year [5]. This new class peptide antibiotics, called Odilorhabdins (ODLs), are produced by *Xenorhabdus nematophoila*, an entomopathogenic bacteria that have a mutual relationship with nematodes [5]. ODLs released by *Xenorhabdus nematophilia* are primarily used to prevent other competing bacteria and fungi invade the insect's corpse and gave time for the nematode to absorb the nutrients from the insect's corpse during the macromolecular degradation [5].

ODLs are encoded by non-ribosomal peptide synthetases (NRPSs) gene cluster that is present in *Xenorhabdus nematophilia*. The NRPSs gene cluster is well known for its function in Gram-positive actinomycetes as the source of antibiotics from the secondary metabolites [5]. Therefore, Lucile *et al.* tried to elucidate the secondary metabolite that is produced by *Xenorhabdus nematophilia* and they found ODLs [5].

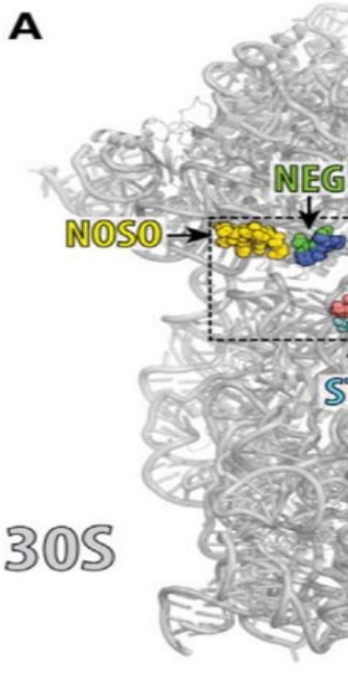


Figure 2. Antibiotics that Bir
(STR, cyan), Paromomycin (

Unlike Teixobactin, ODLs are peptide antibiotics that bind with the decoding center of the small subunit of the bacterial ribosome [5]. This property makes ODLs as the broad-spectrum antibiotic that is effective for both Gram-positive and Gram-negative bacteria [5]. Unlike the other ribosome-targeting antibiotic, ODLs binds to at a new site in small ribosomal subunit that is not exploited by other antibiotics which makes it exceptional (Figure2) [5]. After ODLs bind with the rRNA and tRNA, it will stimulate miscoding in the cell-free trans-

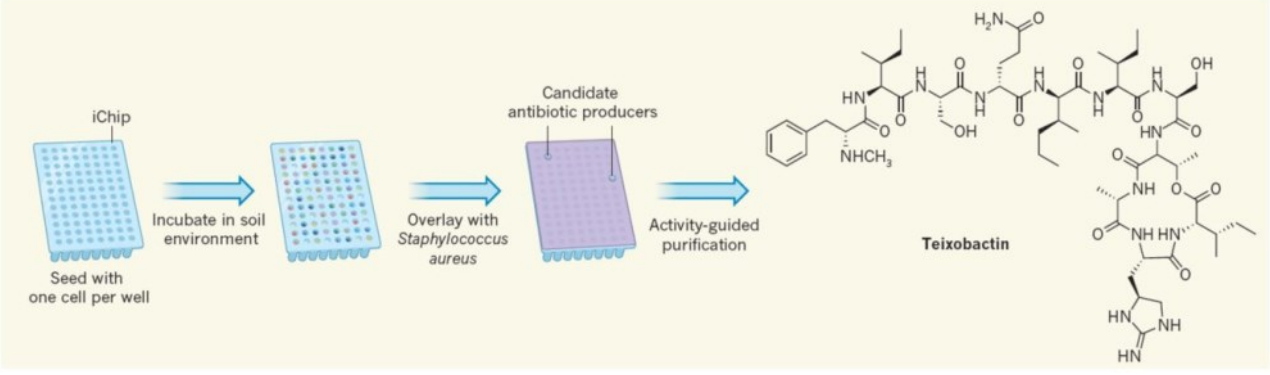
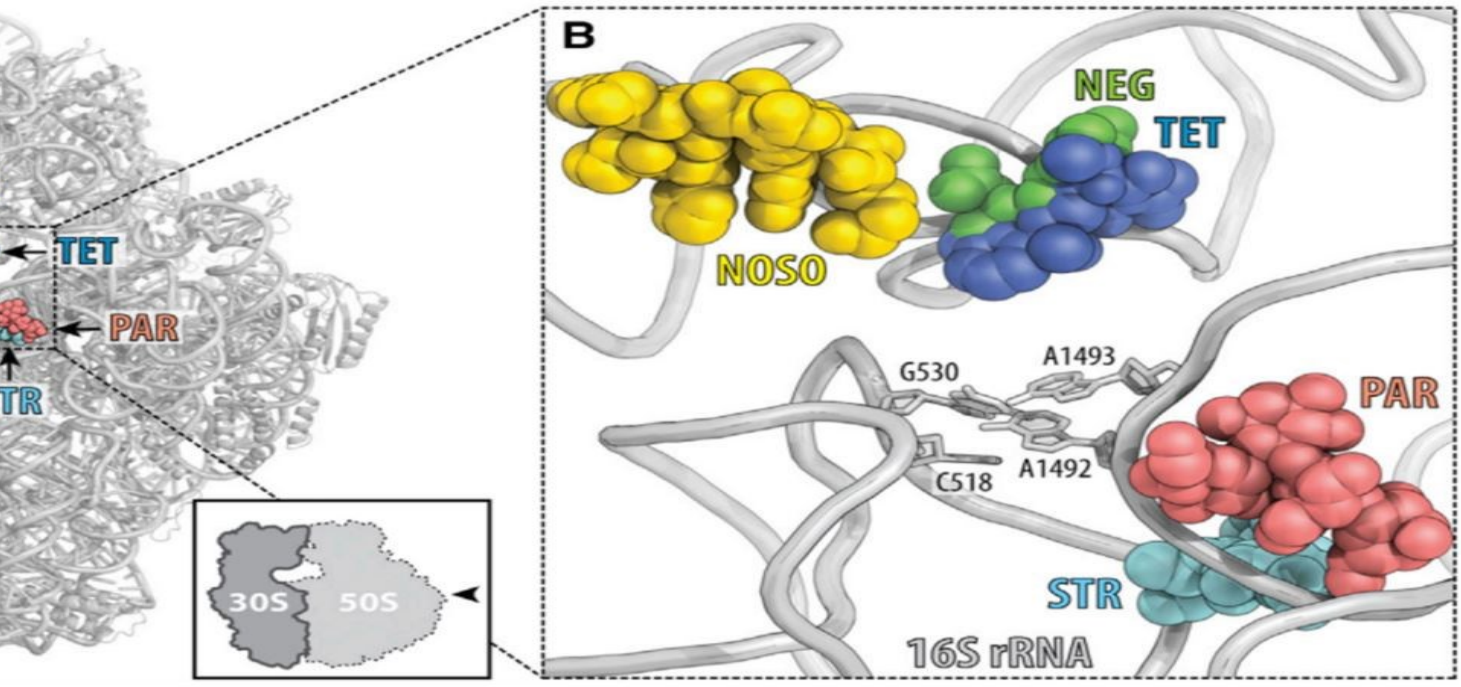


Figure1. iChip technology that has been used to identify *Eleftheria terrae* as the producer of Teixobactin [4].



nd in the Decoding Center on the Small Ribosomal Subunit (A and B). NOSO (Odilorhabdins, yellow), Streptomycin PAR, salmon), Tetracycline (TET, blue), and Negamycin (NEG, green) [5].

lation system and protein synthesis [5].

NOSO-502, the first clinical candidate of ODLs candidates, has shown promising results in vitro and in vivo in the mouse model [6, 7]. NOSO-502 is active against a panel of Gram-positive and Gram-negative bacteria, including carbapenem-resistant and polymyxin-resistant bacteria in vitro [7]. In addition, there was no cytotoxicity against HepG2, HK-2, or HRPT cells which suggested the favourable safety profile of NOSO-502. The plasma levels of NOSO-502 are stable when tested to mouse, rat, dog, monkey, and human plasma [7]. Moreover, the efficacy was tested in murine infection models and proven effective against Gram-negative pathogens including *Eschericia coli* and *Klebsiella pneumoniae* [6, 7].

Two new classes of antibiotics have been discovered in the past five years, but both antibiotics still need to be thoroughly investigated for their therapeutic potential and safety profile. The development of new antibiotics as the last resort to combat AMR is a critical subject for healthcare researchers around the world including Indonesia.

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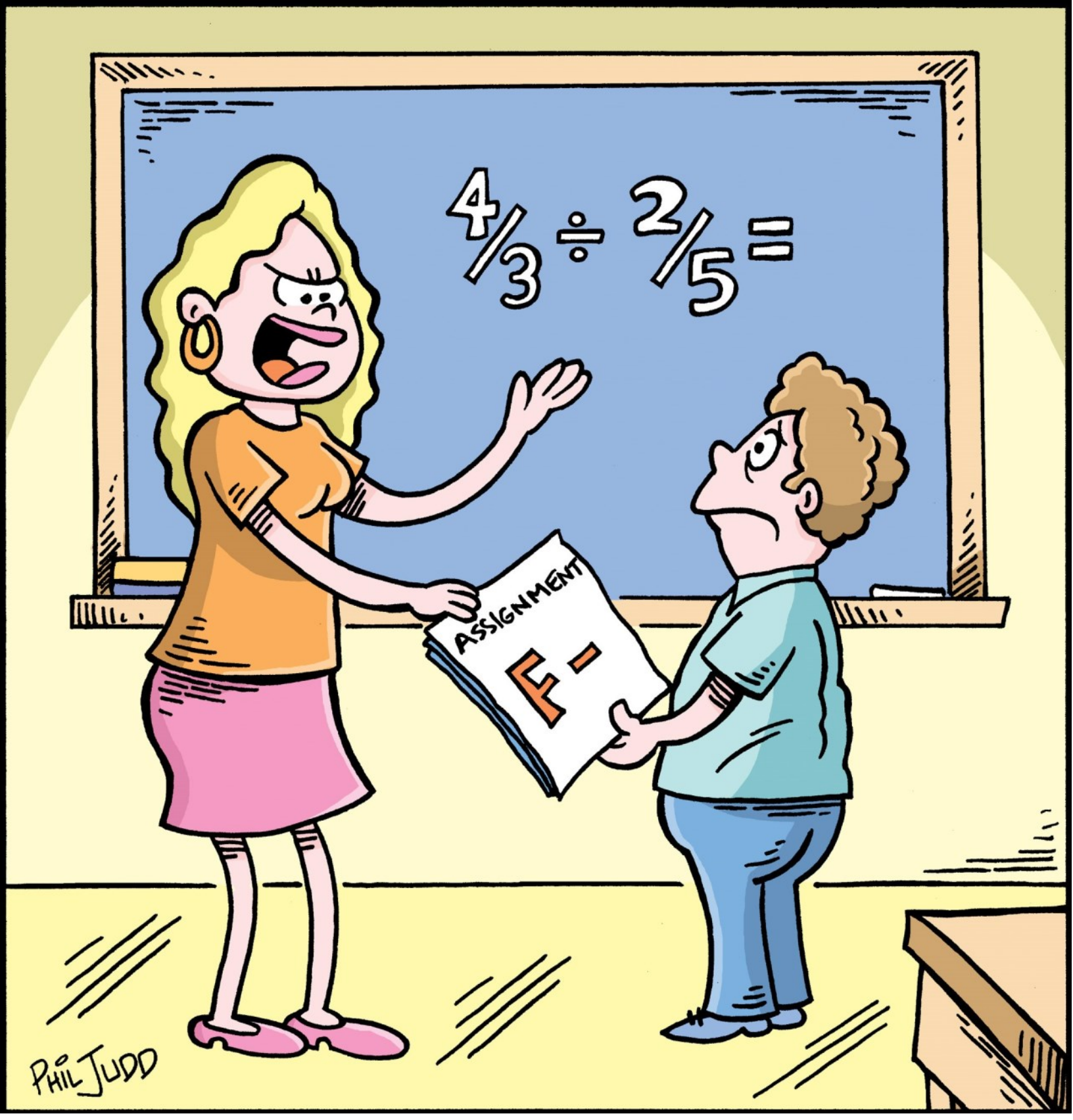

“No Jimmy! You can’t cite Wikipedia as the main source for your assignment!”

INA-RESPOND Newsletter

The Art of Using Wikipedia for Research

By: ALY DIANA

Yes, there is a big stamp on Wikipedia which says that it is not a credible/reliable source for academic citation. The unique thing with Wikipedia is anyone may edit an article, deleting accurate information or adding false information – which is one of the many factors Wikipedia can keep growing. It provides free knowledge from mostly unpaid contributors (as long as you can get an access to internet and proper gadget). However, lack of responsibilities of the author(s) of a Wiki's article seems to create a substantial amount of doubt to deny its validity to join other peer-review sources as an academic citation.

Wikipedia itself provides some useful articles about this particular topic, for example: "Researching with Wikipedia", "Wikipedia: Academic Use", and "Reliability of Wikipedia". Amazingly, increasing number of university libraries also provide guides on using, editing, and contributing to Wikipedia. Some acknowledge Wikipedia as "one of the largest open educational resources in the world", which is somewhat true. In general, the articles in Wikipedia can help us with our research by gathering background information on a topic, using the references to broaden our search on the topic and generate search terms that could be used when searching the library or a database. The main advantage of reading a Wikipedia article is that it gives a quick access to a lot of information, and the information can mostly be digested well because it is written in a colloquial language.

The most important thing when we are reading an article in Wikipedia (or in any sources, really) is to keep our critical mind. Nothing can be considered a fact until it has been confirmed. Starting to gain knowledge through Wikipedia, especially on a topic that is beyond our own expertise, is a good practice to maintain and improve our ability in exercising our critical appraisal.

So far, we have come to understand what Wikipedia is and covered its strengths and weaknesses. We have also talked about how to use Wikipedia wisely for our academic research. Considering how Wikipedia is widely used and accessed by people around the world to get information, contributing in this massive growing source of information and sharing our own expertise to create better and more accurate articles is encouraged by more and more universities. Researchers and scholars can contribute by editing existing entries and/or creating new ones. This is actually a good way to share our knowledge and provide sound scientific facts to wider audiences. At the very least, it provides a chance for us to practice.

I believe that this is a very simple article with a clear conclusion, regardless the debates out there about citing vs. not citing Wikipedia. In addition, if you have the time, these useful links may provide you with extra information related to this issue.

http://guides.library.cornell.edu/wikipedia and http://libguides.library.nuigalway.ie/wikipedia.

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INA-RESPOND website: www.ina-respond.net

INA-RESPOND Newsletter

The Indonesia Research Partnership on Infectious Disease newsletter is an internal bulletin of INA-RESPOND research network intended to disseminate information related to the network's studies, activities, and interests to all members of the network as well as its sponsors and related parties.

The INA-RESPOND newsletter welcomes all network members and stakeholders to contribute by submitting articles related to the network's studies and interests. Send your articles or subscribe to our latest newsletter by sending an email to INA.Secretariat@ina-respond.net