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2021

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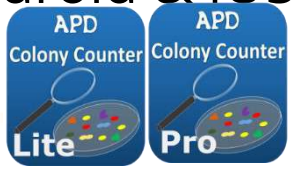

DNAApp

DNA2App
Sequence Analyzer

VibraTilt
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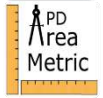

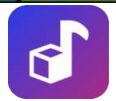

Desktop, App, & Website

CREATING GROWTH, ENHANCING LIVES

Commentary: Augmented Reality Scientific Phone Apps – making the APD AR Holistic Review app and using existing AR apps for scientific publications

Jun-Jie Poh[1,3], Ser-Xian Phua[1], Kwok-Fong Chan[1], Samuel Ken-En Gan[1,2,3,*]

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INTRODUCTION

The average scientific publication is not the most palatable of reading materials, especially to those not in the relevant disciplines. Yet, conveying scientific concepts easily is precisely what scientific publications are meant to do. Imagine what the use of video pictures/paintings as depicted in the Harry Potter movie series can do to make things easier!

While the fantasy of moving photos/pictures does not exist physically in the real world, just as Santa Claus cannot travel the world today without being shot down by anti-missiles, there are some and entertainment, AR has yet to penetrate fully into scientific publications where it can play an important role to address the difficulty of squeezing three-dimensional (3D) ideas into the traditional two-dimensional (2D) graphics on screen/paper.

AR APPLICATION TO SCIENTIFIC PUBLISHING

Scientific publishing is the bread and butter of academic research for the sciences, and the onus is on the authors to convey their work to the scientific community and the general public (Gan, 2018a, 2018b). Beyond academic research, it is

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Methods

Augmented reality in scientific visualization and communications: a new dawn of looking at antibody interactions

Kwok-Fong Chan[1], Jun-Jie Poh[1], Wei-Ling Wu[1] and Samuel Ken-En Gan[1,2,3,*]

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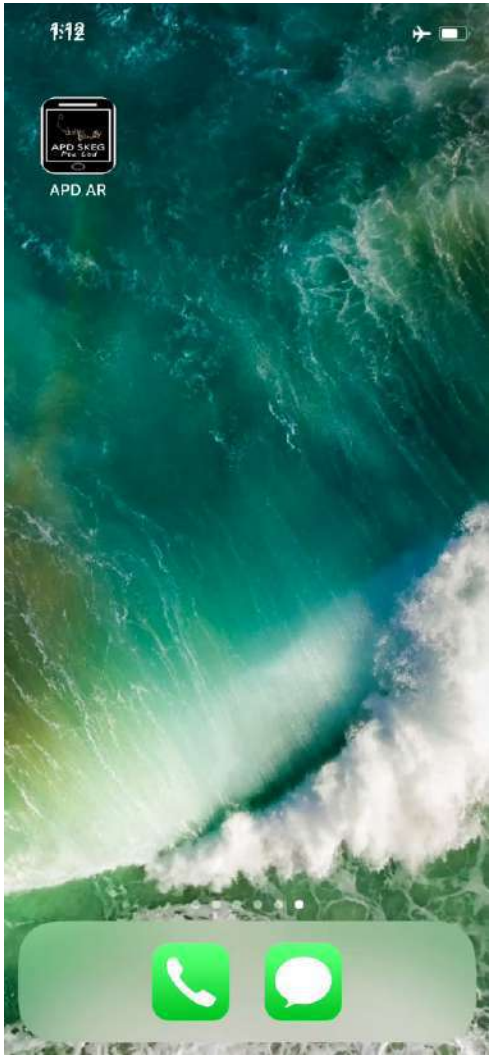
Abstract

The use of augmented reality (AR) in providing three-dimensional (3D) visual support and image depth have been applied in education, tourism, historical studies, and medical training. In research and development, there has been a slow but growing use of AR tools in chemical and drug discovery, but little has been implemented for whole 3D antibody structures (IgE, IgM, IgA, IgG, and IgD) and in communicating their interactions with the antigens or receptors in publications. Given that antibody interactions can vary significantly between different monoclonal antibodies, a convenient and easy to use 3D visualization can convey structural mechanisms clearer to readers, especially in how residues may interact with one another. While this was previously constrained to the use of stereo images on printed material or molecular visualization software on the computer, the revolution of smartphone and phablets now allows visualization of whole molecular structures on-the-go, allowing rotations, zooming in and out, and even animations without complex devices or the training of visual prowess. While not yet as versatile as molecular visualization software on the computer, such technology is an improvement from stereo-images and bridges the gap with molecular visualization tools. In this report, we discuss the use of AR and how they can be employed in the holistic view of antibodies and the future of the technology for better scientific communication.

Statement of Significance: Recent technological progress has allowed augmented visualization of three-dimensional antibody structures using mobile devices. This allows an on-the-go convenient visual appreciation of the antibody elements and how the various antibody regions can interact with each other in a new frontier of communicating antibody research that can extend to all structural biology.



methods and protocols

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Vol. 3 (2020) Vol. 1 (2018)

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SCIENTIFIC REPORTS

OPEN

The effects of Antibody Engineering CH and CL in Trastuzumab and Pertuzumab recombinant models: Impact on antibody production and antigen-binding

Received: 9 June 2017
Accepted: 19 December 2017
Published online: 15 January 2018

Wai-Heng Lua[1], Wei-Li Ling[1], Joshua Yi Yeo[1], Jun-Jie Poh[1], David Philip Lane[1,2] & Samuel Ken-En Gan[1,2]

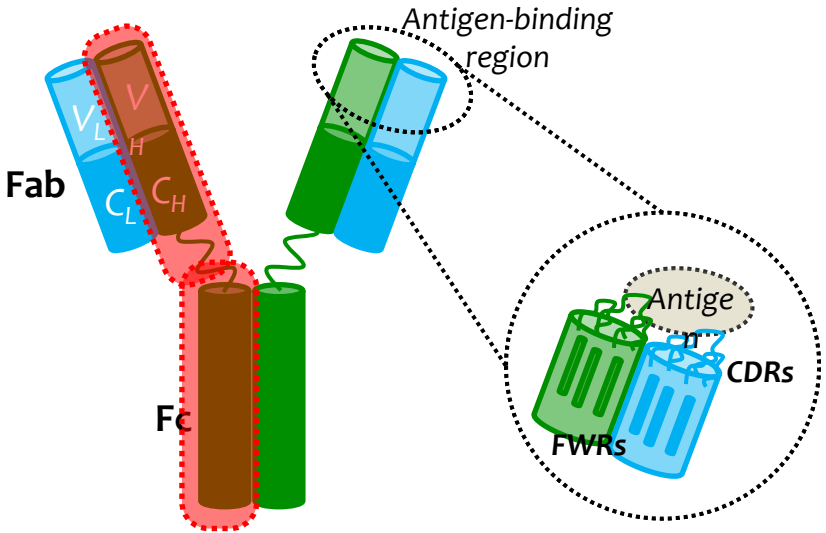
Current therapeutic antibodies such as Trastuzumab, are typically of the blood circulatory IgG1 class (Cκ/ CH-γ1). Due to the binding to Her2 also present on normal cell surfaces, side effects such as cardiac failure can sometimes be associated with such targeted therapy. Using antibody isotype swapping, it may be possible to reduce systemic circulation through increased tissue localization, thereby minimising unwanted side effects. However, the effects of such modifications have yet to be fully characterized, particularly with regards to their biophysical properties in antigen binding. To do this, we produced all light and heavy chain human isotypes/subtypes recombinant versions of Trastuzumab and Pertuzumab, and studied them with respect to recombinant production and Her2 binding. Our findings show that while the light chain constant region changes have no major effects on production or Her2 binding, some heavy chain isotypes, in particularly, IgM and IgD isotypes, can modulate antigen binding. This study thus provides the groundwork for such isotype modifications to be performed in the future to yield therapeutics of higher efficacy and efficiency.

The "new dawn"[1] of therapeutics had come with recombinant monoclonal antibodies (mAbs). Most approved clinical therapeutic mAbs are of the Cκ and Cγ1 isotypes, notably Trastuzumab and Pertuzumab which have significant combined success in the treatment of Her2 + cancers[2]. However, when bound to normal Her2 expressing cardiac cells, Trastuzumab can cause side effects such as cardiac failure[3]. To reduce such side effects, one possible solution is to improve the antibody localization to the cancer target areas, reducing systemic circulation. Such efforts can be actualized by engineering a change of the antibody isotype through recombinant means, especially since the general localization of these antibody isotypes are already well established in classic immunology. On this possibility, there is great interest in utilizing isotypes for immunotherapy, particularly for cancer[4].

The human immunoglobulin (Ig) heavy chain isotypes and subtypes (CH variants) consist of IgM, IgA1, IgA2, IgD, IgG1, IgG2, IgG3, IgG4, and IgE. Of the CH variants, the most abundant is the IgG isotype in which IgG1 is the most dominant subtype in blood. IgM, like IgG, is also predominantly localized in blood and both isotypes exhibit specialized immune functions such as Antibody Dependent Cell-mediated Cytotoxicity (ADCC)[5]. Given its role in neutralizing infectious agents[5] and activating the complement system amongst the recruitment of immune cells, IgG, particularly IgG1, is the default choice for therapeutic monoclonal antibodies.

Nonetheless, there has been increasing interest in exploring the use of alternative CH variants as therapeutic antibodies. Two such examples include IgA[6] and IgE[7], along with their immune activation mechanisms[8,9]. With the prowess of these CH variants to also elicit immune responses at a level comparable to IgG, there are potential advantages in using these CH variants when considering their localization in tissues or organs of interest.

IgM, the primary antibody responsible for defense against new antigens, is often found as an oligomer (pentamer or hexamer) with or without the J-chain. It functions to agglutinate and immobilize antigens[10] as well



Lua *et al.*, Sci.Rep 2018

ACCEPTED MANUSCRIPT

Sagacity in Antibody humanization for therapeutics, diagnostics and research purposes: Considerations of antibody elements and their roles.

Wei-Li Ling, Wai-Heng Lua, Samuel Ken-En Gan ✉

Antibody Therapeutics, tbaa005, https://doi.org/10.1093/abt/tbaa005
Published: 18 April 2020

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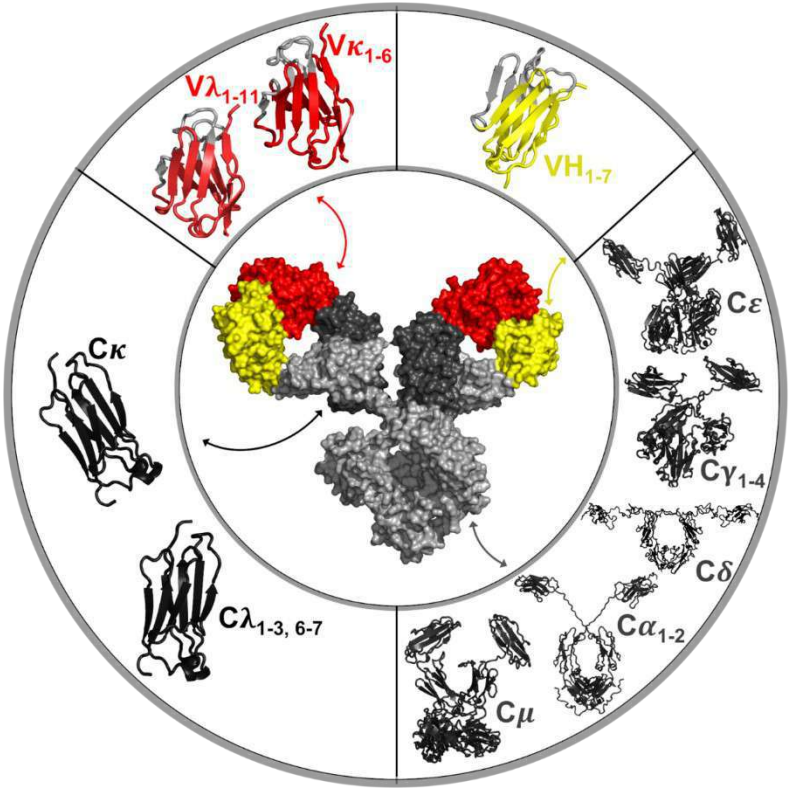
Abstract

The humanization of antibodies for therapeutics is a critical process that can determine the success of antibody drug development. However, the science underpinning this process remains elusive with different laboratories having very different methods. Well-funded laboratories can afford automated high throughput screening methods to derive their best binder regardless of many other parameters, yet this often involves a very expensive initial set of equipment affordable only to a few. Often within these high-throughput processes, only standard key parameters such as production, binding, and aggregation can and are analysed. Given the lack of suitable animal models, it is only at clinical trials can immunogenicity and allergy adverse effects be detected through anti-human antibodies as per FDA guidelines. While some occurrences that slip through can be mitigated by additional desensitization protocols, such adverse reactions to grafted humanized antibodies can be prevented at the humanization step. Considerations such as better antibody localization, avoidance of unspecific interactions to superantigens, and the tailoring of antibody dependent triggering of immune responses, the antibody persistence on cells, can all be considered through a holistic sagacious approach, allowing for better outcomes for therapy and even for research and diagnostic purposes.



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Localization of antibodies

Day 1

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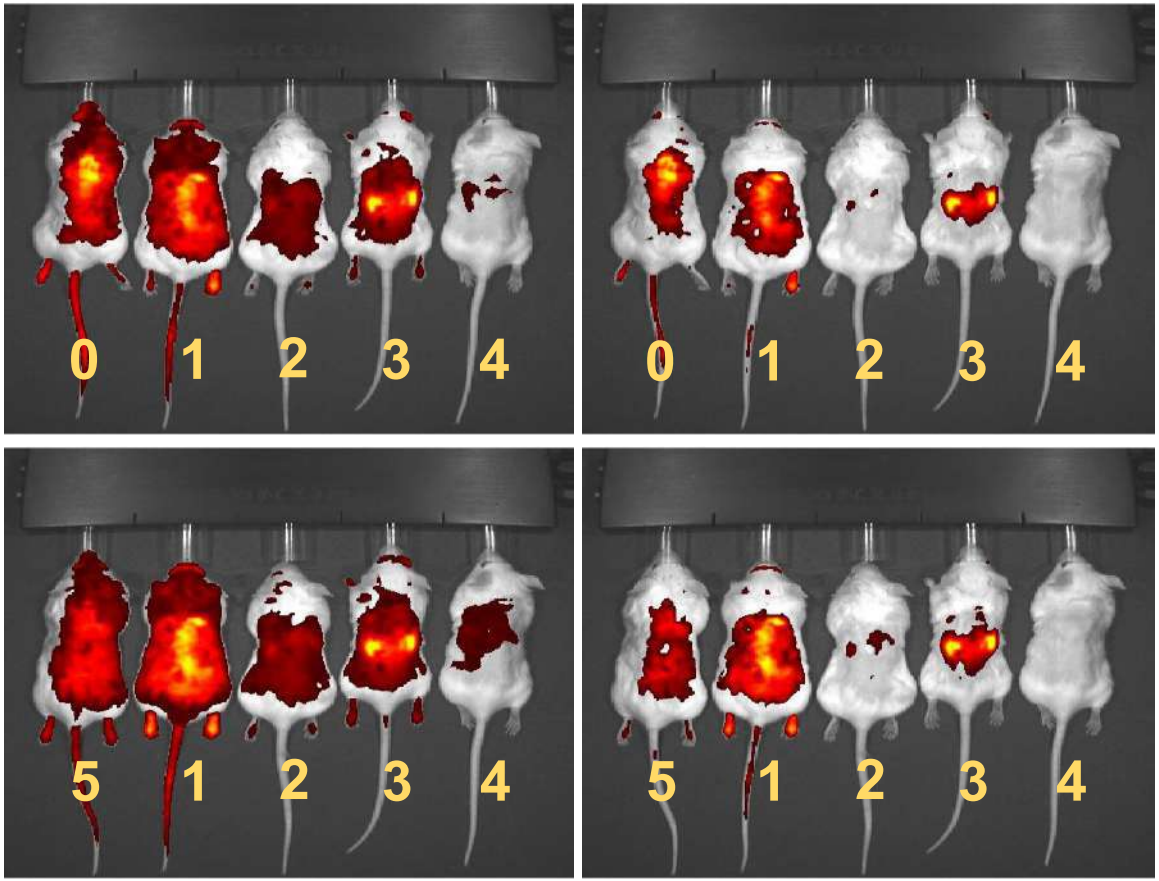
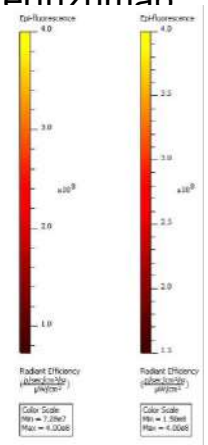


0- Trastuzumab
1- IgG
2- IgA
3- IgD
4- IgE
5- Pertuzumab



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Mice work by p53Lab Koh XY, KohXH

Day 3

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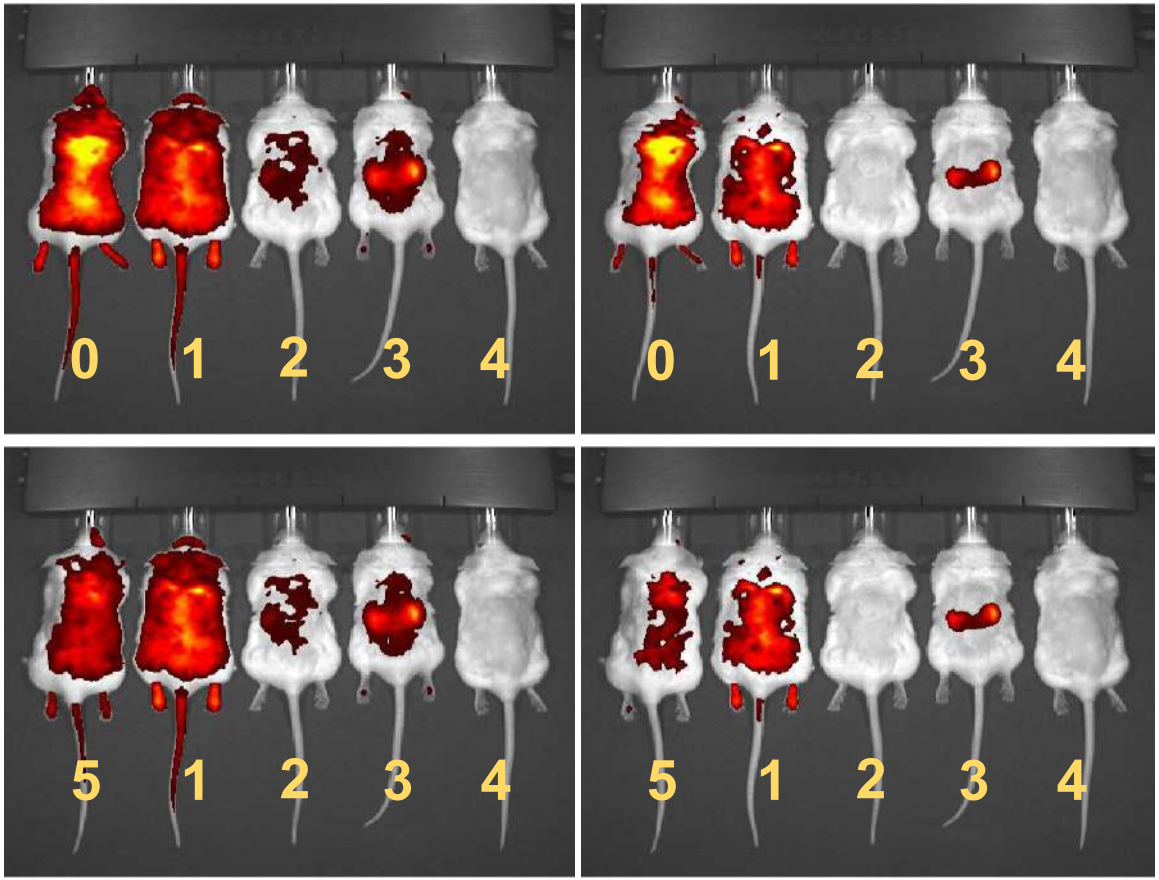
Low background



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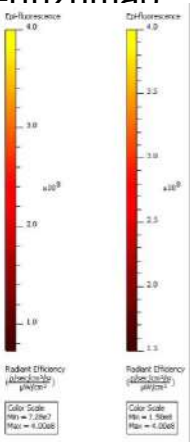

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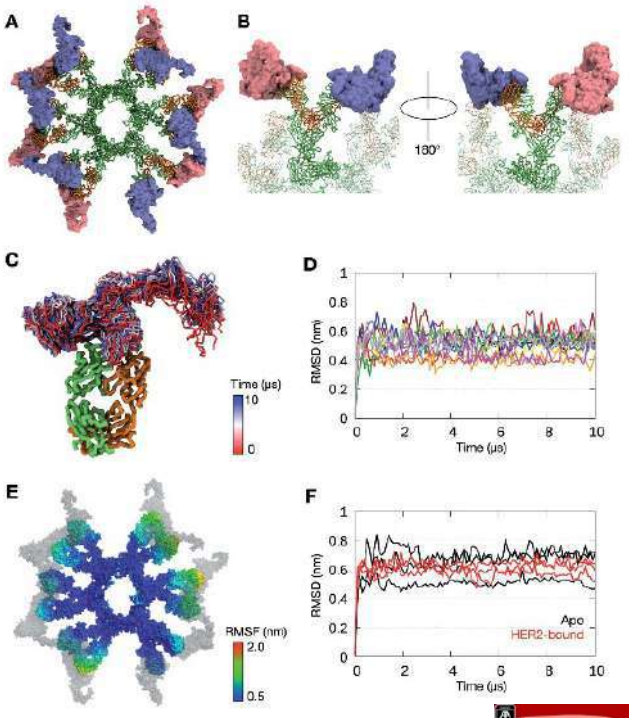

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Cite this: DOI: 10.1039/c9sc04722k

All publication charges for this article have been paid for by the Royal Society of Chemistry

Not all therapeutic antibody isotypes are equal: the case of IgM *versus* IgG in Pertuzumab and Trastuzumab†

Firdaus Samsudin,[a] Joshua Yi Yeo,[a] Samuel Ken-En Gan *[acd] and Peter J. Bond*[ab]

The therapeutic potential of immunoglobulin M (IgM) is of considerable interest in immunotherapy due to its complement-activating and cell-agglutinating abilities. Pertuzumab and Trastuzumab are monoclonal antibodies used to treat human epidermal growth factor receptor 2 (HER2)-positive breast cancer but exhibit significantly different binding affinities as IgM when compared to its IgG isotype. Using integrative multiscale modelling and simulations of complete antibody assemblies, we show that Pertuzumab IgM is able to utilize all of its V-regions to bind multiple HER2 receptors simultaneously, while similar binding in Trastuzumab IgM is prohibited by steric clashes caused by the large globular domain of HER2. This is subsequently validated by confirming that Pertuzumab IgM inhibits proliferation in HER2 over-expressing live cells more effectively than its IgG counterpart and Trastuzumab IgM. Our study highlights the importance of understanding the molecular details of antibody–antigen interactions for the design and isotype selection of therapeutic antibodies.

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DOI: 10.1039/c9sc04722k

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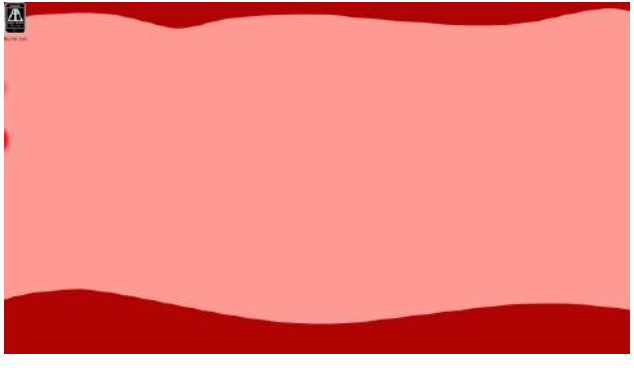
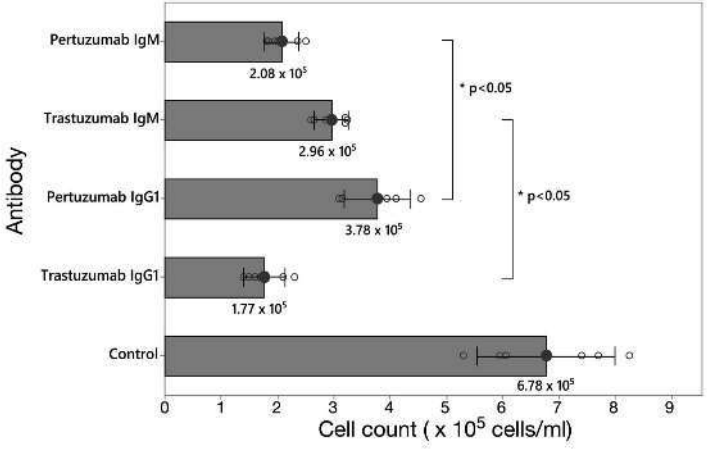




THE JOURNAL OF Allergy AND Clinical Immunology

Article in Press

Role of the IgE variable heavy chain in FcεRIα and superantigen binding in allergy and immunotherapy

Wai-Heng Lua, BSc[a,*], Chinh Tran-To Su, PhD[a,*], Joshua Yi Yeo, Dip[a], Jun-Jie Poh, Dip[a], Wei-Li Ling, BSc[a], Ser-Xian Phua, Dip[a], Samuel Ken-En Gan, PhD[a,b,*]

Open Access PlumX Metrics
DOI: https://doi.org/10.1016/j.jaci.2019.03.028
Article Info

The Editors' Choice

Zuhair K. Ballas, MD
and the Associate Editors of the JACI

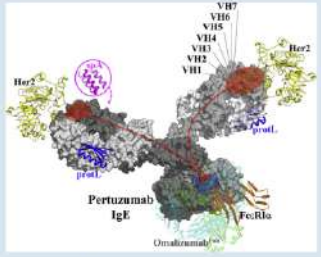
THE JOURNAL OF Allergy AND Clinical Immunology
VOLUME 144 NUMBER 2

Whole IgE matters! Implications in allergo-oncology and allergen-specific IgE overrepresentation?

Binding of IgE to its high-affinity FcεRIα receptor subunit is often assumed to be consistent across IgEs. Thus many allergy studies that investigate the role of IgE in allergy were focused on Fab or Fc regions. Using the therapeutic antibodies pertuzumab and trastuzumab as models for studying the IgE molecule holistically, Lua et al (p 514) demonstrated the importance of whole-antibody investigations, as summarized in the figure below. Their study had the following key findings:

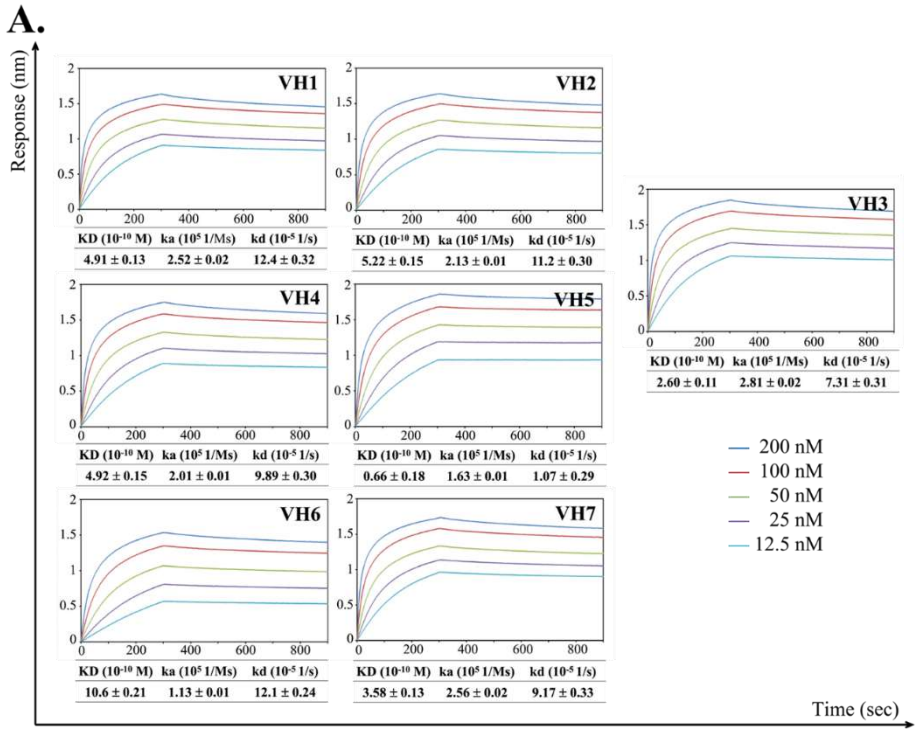
- IgE V-regions can modulate the IgE Fc-FcεRIα interaction, but there was no notable effect on omalizumab binding to IgE Fc.
- Interaction with protein A superantigen, which previously was reported to be caused by the VH3 framework, also was modulated by minor changes in V-region complementarity-determining regions.

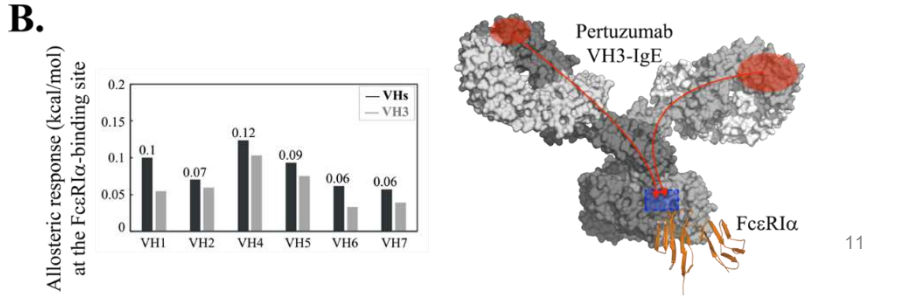
These results may explain the overrepresentation of specific IgE populations on sensitized effector cells in allergy pathogenesis.



The effects of VH families on a pertuzumab IgE model with its effects on FcεRIα, omalizumab, and protein A interaction.

Therapeutic IgE antibodies in allergo-oncology can be engineered to avoid superantigen activation.





antibodies

MDPI

Article

Allosteric Effects between the Antibody Constant and Variable Regions: A Study of IgA Fc Mutations on Antigen Binding

Chinh Tran-To Su [1,‡], Wai-Heng Lua [1,‡], Wei-Li Ling [1] and Samuel Ken-En Gan [1,2,*]

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‡ Authors equally contributed to the work.

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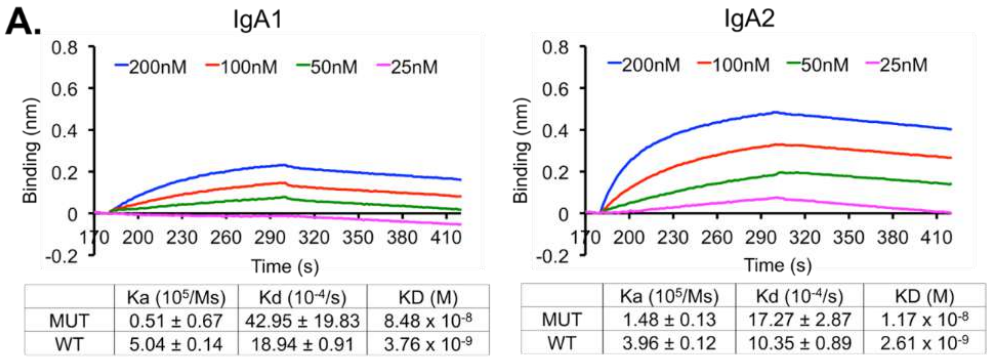
Abstract: Therapeutic antibodies have shifted the paradigm of disease treatments from small molecules to biologics, especially in cancer therapy. Despite the increasing number of antibody candidates, much remains unknown about the antibody and how its various regions interact. Recent findings showed that the antibody constant region can govern localization effects that are useful in reducing side effects due to systemic circulation by the commonly used IgG isotypes. Given their localized mucosal effects, IgA antibodies are increasingly promising therapeutic biologics. While the antibody Fc effector cell activity has been a focus point, recent research showed that the Fc could also influence antigen binding, challenging the conventional idea of region-specific antibody functions. To investigate this, we analysed the IgA antibody constant region and its distal effects on the antigen binding regions using recombinant Pertuzumab IgA1 and IgA2 variants. We found that mutations in the C-region reduced Her2 binding experimentally, and computational structural analysis showed that allosteric communications were highly dependent on the antibody hinge, providing strong evidence that we should consider antibodies as whole proteins rather than a sum of functional regions.

Keywords: antibody; isotype IgA; Pertuzumab; allosteric; biologics; constant region; variable region

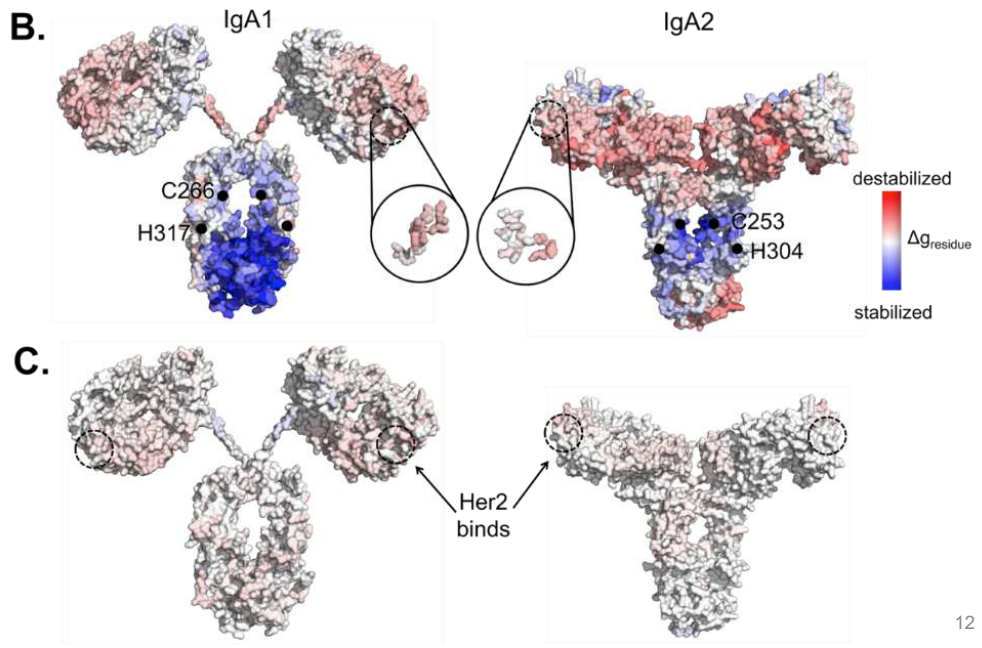
1. Introduction

Antibodies, called the "magic bullet" by Paul Erhlich [1–3], have shown great promise as therapeutic agents against numerous diseases [4], with many breakthroughs documented [5–10]. One promising isotype is IgA, whose predominant mucosal activation and localization can reduce



	Ka (10^5/Ms)	Kd (10^{-4}/s)	KD (M)
MUT	0.51 ± 0.67	42.95 ± 19.83	8.48 x 10^{-8}
WT	5.04 ± 0.14	18.94 ± 0.91	3.76 x 10^{-9}

	Ka (10^5/Ms)	Kd (10^{-4}/s)	KD (M)
MUT	1.48 ± 0.13	17.27 ± 2.87	1.17 x 10^{-8}
WT	3.96 ± 0.12	10.35 ± 0.89	2.61 x 10^{-9}



frontiers in Immunology

ORIGINAL RESEARCH
published: 07 December 2020
doi: 10.3389/fimmu.2020.604318

Essentially Leading Antibody Production: An Investigation of Amino Acids, Myeloma, and Natural V-Region Signal Peptides in Producing Pertuzumab and Trastuzumab Variants

*Wei-Li Ling[1,2,3], Chinh Tran-To Su[1,3], Wai-Heng Lua[1], Jun-Jie Poh[1], Yuen-Ling Ng[2], Anil Wipat[4] and Samuel Ken-En Gan[1,3]**

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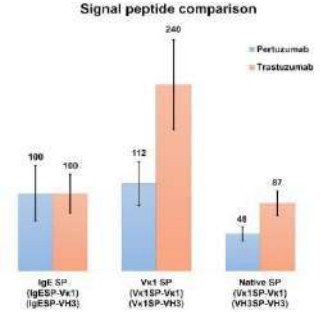
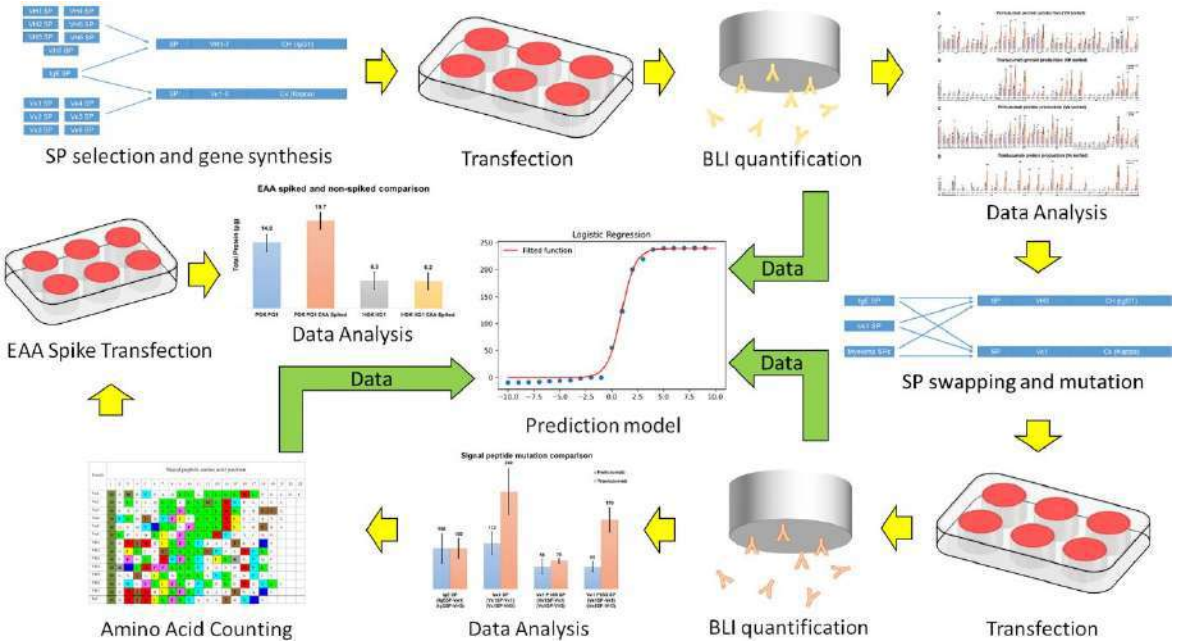
Specialty section:
This article was submitted to B Cell Biology, a section of the journal Frontiers in Immunology

Boosting the production of recombinant therapeutic antibodies is crucial in both academic and industry settings. In this work, we investigated the usage of varying signal peptides by antibody V-genes and their roles in recombinant transient production, systematically comparing myeloma and the native signal peptides of both heavy and light chains in 168 antibody permutation variants. We found that amino acids count and types (essential or non-essential) were important factors in a logistic regression equation model for predicting transient co-transfection protein production rates. Deeper analysis revealed that the culture media were often incomplete and that the supplementation of essential amino acids can improve the recombinant protein yield. While these findings are derived from transient HEK293 expression, they also provide insights to the usage of the large repertoire of antibody signal peptides, where by varying the number of specific amino acids in the signal peptides attached to the variable regions, bottlenecks in amino acid availability can be mitigated.





Bioscience Reports (2019) **39** BSR20181958
https://doi.org/10.1042/BSR20181958

PORTLAND PRESS

Perspective

Perspective: The promises of a holistic view of proteins—impact on antibody engineering and drug discovery

Ser-Xian Phua[1], Kwok-Fong Chan[1], Chinh Tran-To Su[1], Jun-Jie Poh[1,2] and Samuel Ken-En Gan[1,2,3]

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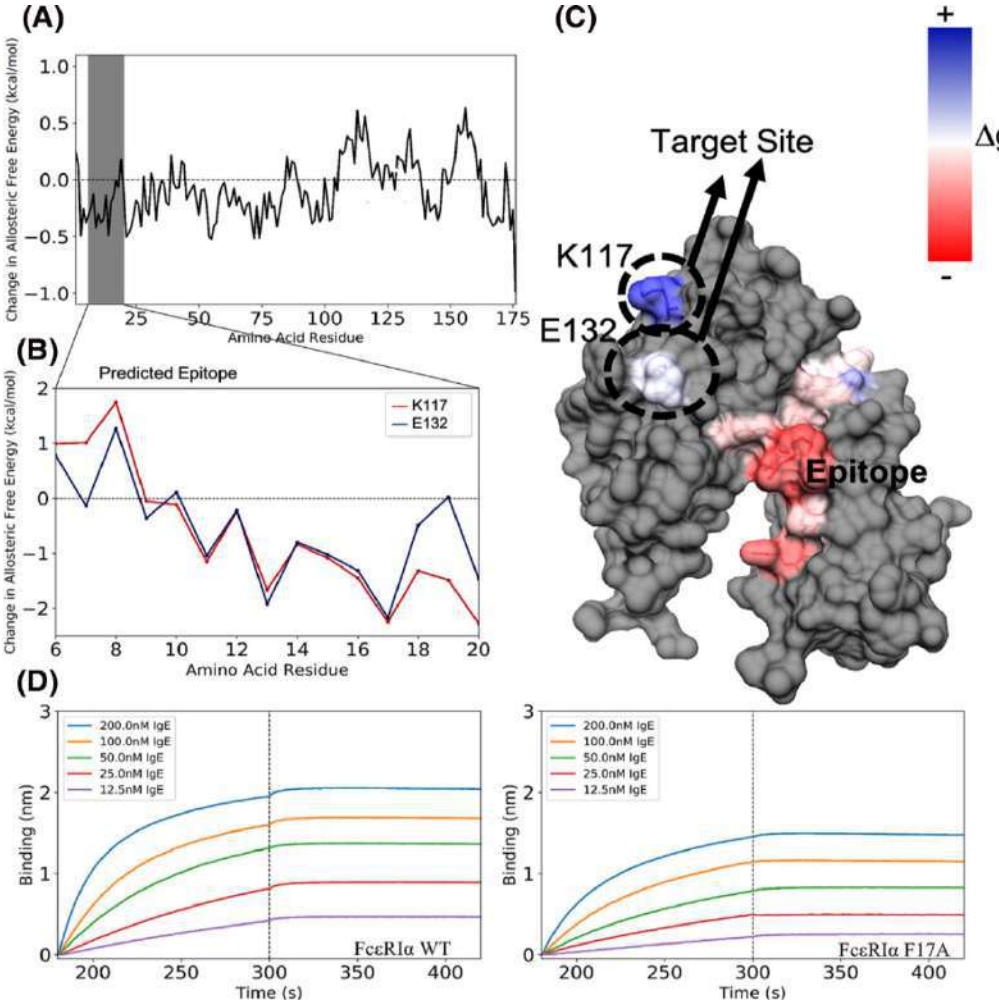
The reductionist approach is prevalent in biomedical science. However, increasing evidence now shows that biological systems cannot be simply considered as the sum of its parts. With experimental, technological, and computational advances, we can now do more than view parts in isolation, thus we propose that an increasing holistic view (where a protein is investigated as much as a whole as possible) is now timely. To further advocate this, we review and discuss several studies and applications involving allostery, where distant protein regions can cross-talk to influence functionality. Therefore, we believe that an increasing big picture approach holds great promise, particularly in the areas of antibody engineering and drug discovery in rational drug design.



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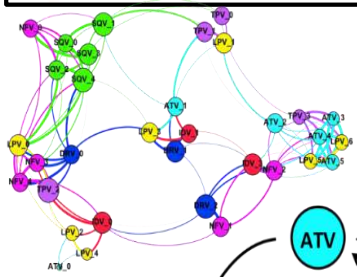

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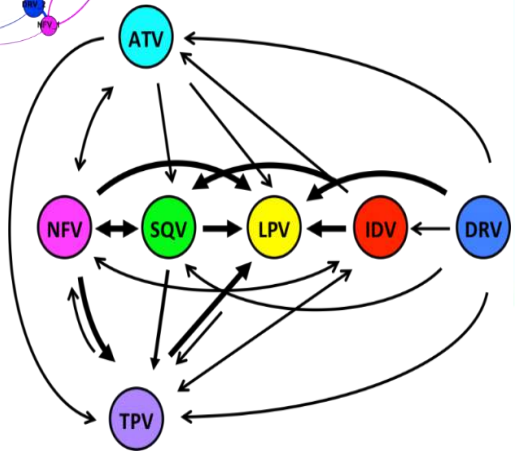

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BMC Bioinformatics

RESEARCH Open Access

Structural analyses of 2015-updated drug-resistant mutations in HIV-1 protease: an implication of protease inhibitor cross-resistance

Chinh Tran-To Su[1*], Wei-Li Ling[1], Wai-Heng Lua[1], Yu-Xuan Haw[1] and Samuel Ken-En Gan[1,2*]

From 15th International Conference On Bioinformatics (INCOB 2016)
Queenstown, Singapore. 21-23 September 2016

Abstract

Background: Strategies to control HIV for improving the quality of patient lives have been aided by the Highly Active Anti-Retroviral Therapy (HAART), which consists of a cocktail of inhibitors targeting key viral enzymes. Numerous new drugs have been developed over the past few decades but viral resistances to these drugs in the targeted viral enzymes are increasingly reported. Nonetheless the acquired mutations often reduce viral fitness and infectivity. Viral compensatory secondary-line mutations mitigate this loss of fitness, equipping the virus with a broad spectrum of resistance against these drugs. While structural understanding of the viral protease and its drug resistance mutations have been well established, the interconnectivity and development of structural cross-resistance remain unclear. This paper reports the structural analyses of recent clinical mutations on the drug cross-resistance effects from various protease and protease inhibitors (PIs) complexes.

Methods: Using the 2015 updated clinical HIV protease mutations, we constructed a structure-based correlation network and a minimum-spanning tree (MST) based on the following features: (i) topology of the PI-binding pocket, (ii) allosteric effects of the mutations, and (iii) protease structural stability.

Results and conclusion: Analysis of the network and the MST of dominant mutations conferring resistance to the seven PIs (Atazanavir-ATV, Darunavir-DRV, Indinavir-IDV, Lopinavir-LPV, Nelfinavir-NFV, Saquinavir-SQV, and Tipranavir-TPV) showed that cross-resistance can develop easily across NFV, SQV, LPV, IDV, and DRV, but not for ATV or TPV. Through estimation of the changes in vibrational entropies caused by each reported mutation, some secondary mutations were found to destabilize protease structure. Our findings provide an insight into the mechanism of PI cross-resistance and may also be useful in guiding the selection of PI in clinical treatment to delay the onset of cross drug resistance.

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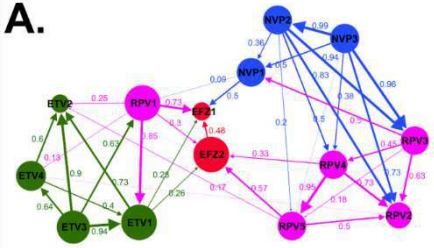
Guide to selection of drugs to delay resistance!

Research Article

A computational study for rational HIV-1 non-nucleoside reverse transcriptase inhibitor selection and the discovery of novel allosteric pockets for inhibitor design

Ron Zhi-Hui Chiang[1], Samuel Ken-En Gan[1,2] and Chinh Tran-To Su[1]

A.



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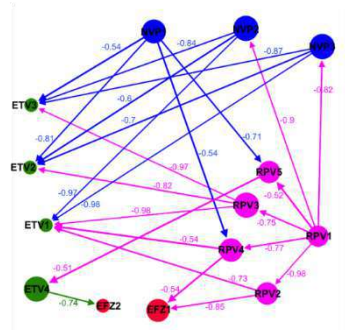

Allosteric targets for broad spectrum antivirals

Research Article

A computational study for rational HIV-1 non-nucleoside reverse transcriptase inhibitor selection and the discovery of novel allosteric pockets for inhibitor design

Ron Zhi-Hui Chiang[1], Samuel Ken-En Gan[1,2] and Chinh Tran-To Su[1]

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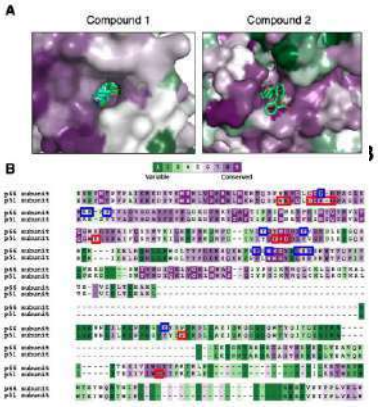

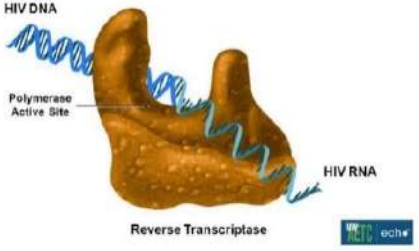

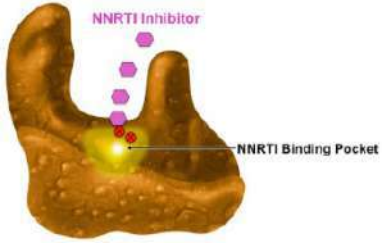

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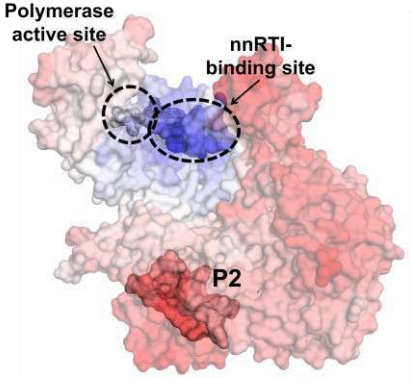

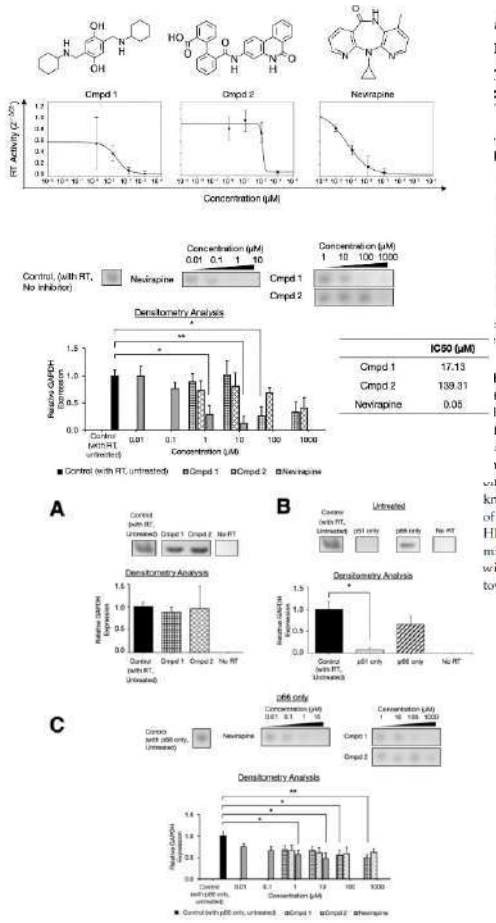

molecules

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n Alternative HIV-1 Non-Nucleoside Reverse anscriptase Inhibition Mechanism: Targeting the 51 Subunit

ok-Fong Chan [1,†], Chinh Tran-To Su [1,2,†], Alexander Krah [1], Ser-Xian Phua [1], hua Yi Yeo [1,2], Wei-Li Ling [1,2], Peter J. Bond [1] and Samuel Ken-En Gan [1,2,3,*]

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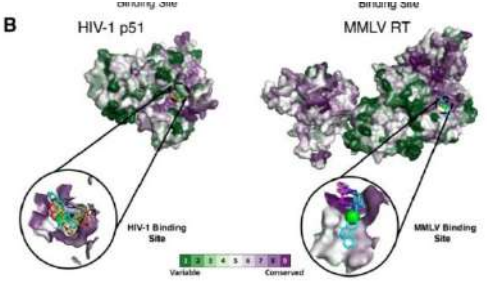
bstract: The ongoing development of drug resistance in HIV continues to push for the need of ternative drug targets in inhibiting HIV. One such target is the Reverse transcriptase (RT) enzyme hich is unique and critical in the viral life cycle—a rational target that is likely to have less off-target fects in humans. Serendipitously, we found two chemical scaffolds from the National Cancer stitute (NCI) Diversity Set V that inhibited HIV-1 RT catalytic activity. Computational structural alyses and subsequent experimental testing demonstrated that one of the two chemical scaffolds inds to a novel location in the HIV-1 RT p51 subunit, interacting with residue Y183, which has no known association with previously reported drug resistance. This finding supports the possibility of a novel druggable site on p51 for a new class of non-nucleoside RT inhibitors that may inhibit HIV-1 RT allosterically. Although inhibitory activity was shown experimentally to only be in the micromolar range, the scaffolds serve as a proof-of-concept of targeting the HIV RT p51 subunit, with the possibility of medical chemistry methods being applied to improve inhibitory activity towards more effective drugs.



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The impact of Gag non-cleavage site mutations on HIV-1 viral fitness from integrative modelling and simulations

Firdaus Samsudin [a], Samuel Ken-En Gan [a,c,d,*], Peter J. Bond [a,b,*]

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Integrative modelling
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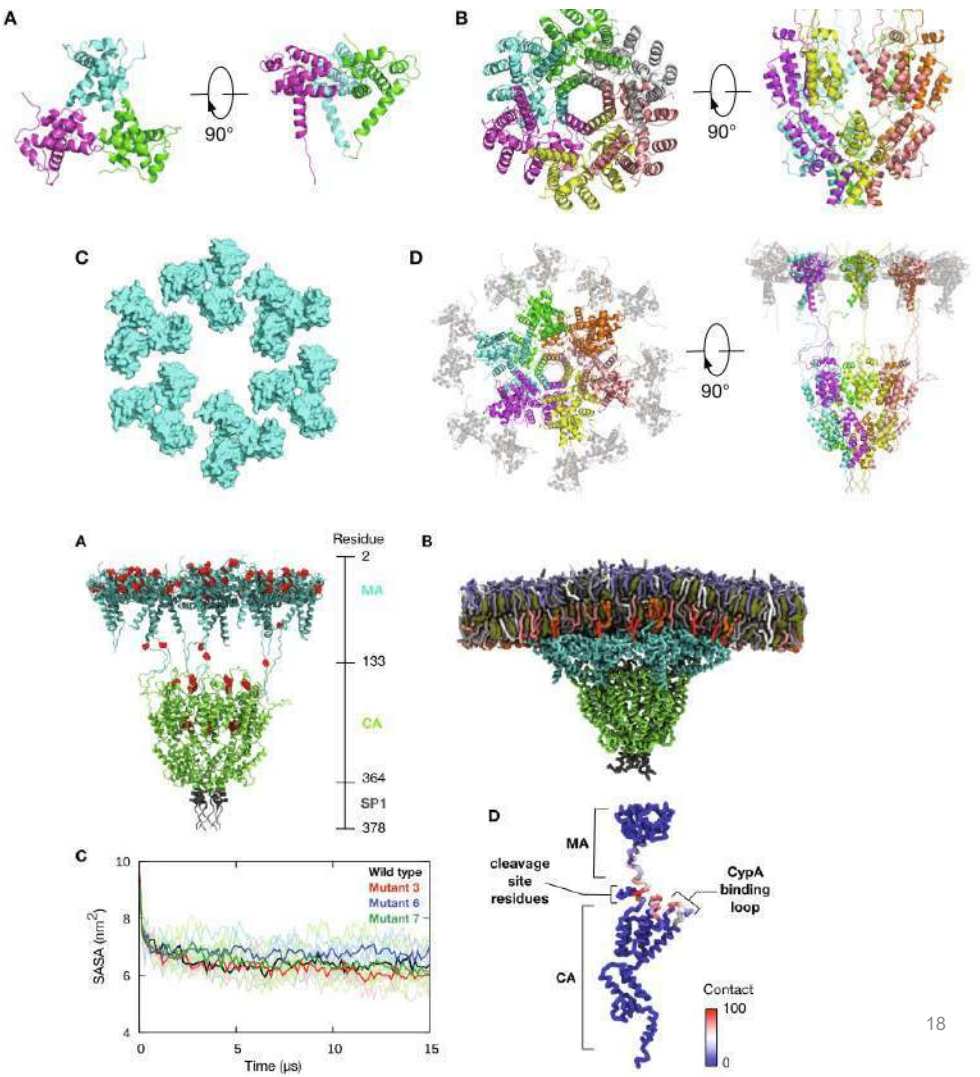
ABSTRACT

The high mutation rate in retroviruses is one of the leading causes of drug resistance. In human immu odeficiency virus type-1 (HIV-1), synergistic mutations in its protease and the protease substrate – t Group-specific antigen (Gag) polyprotein – work together to confer drug resistance against protease inl bitors and compensate the mutations affecting viral fitness. Some Gag mutations can restore Ga protease binding, yet most Gag-protease correlated mutations occur outside of the Gag cleavage si To investigate the molecular basis for this, we now report multiscale modelling approaches to investigate various sequentially cleaved Gag products in the context of clinically relevant mutations that occur outside of the cleavage sites, including simulations of the largest Gag proteolytic product in its viral membrane-bound state. We found that some mutations, such as G123E and H219Q, involve direct interaction with cleavage site residues to influence their local environment, while certain mutations in the matrix domain lead to the enrichment of lipids important for Gag targeting and assembly. Collectively, our results reveal why non-cleavage site mutations have far-reaching implications outside of Gag proteolysis, with important consequences for drugging Gag maturation intermediates and tackling protease inhibitor resistance.



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Probability of change in life: Amino acid changes in single nucleotide substitutions

Kwok-Fong Chan [a,1], Stelios Koukouravas [a,1], Joshua Yi Yeo [a], Darius Wen-Shuo Koh [a], Samuel Ken-En Gan [a,b,c,*]

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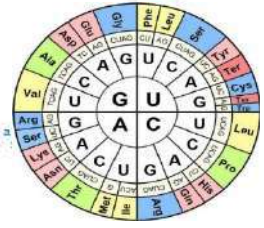

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Codon single base mutation
Single nucleotide substitution
Probability
Amino acid
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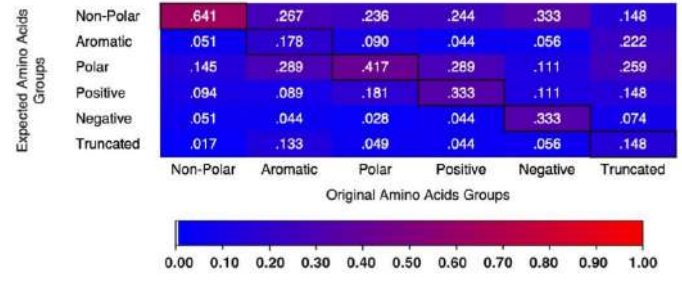
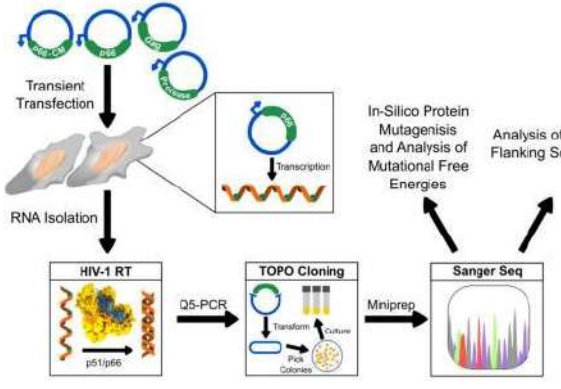
ABSTRACT

Mutations underpin the processes in life, be it beneficial or detrimental. While mutations are assumed to be random in the bereft of selection pressures, the genetic code has underlying computable probabilities in amino acid phenotypic changes. With a wide range of implications including drug resistance, understanding amino acid changes is important. In this study, we calculated the prob[illegible] leading to the 20 amino acids and stop codons. Our ca[illegible] organization of the genetic code that averts disruptive c[illegible] changes include changes to start, aromatic, negative ch[illegible] reveal a statistical mechanism governing the relationshi[illegible]





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Article

Spontaneous Mutations in HIV-1 Gag, Protease, RT p66 in the First Replication Cycle and How They Appear: Insights from an In Vitro Assay on Mutation Rates and Types

Joshua Yi Yeo [1,2], Darius Wen-Shuo Koh [1,2], Ping Yap [1], Ghin-Ray Goh [1] and Samuel Ken-En Gan [1,2,3,*]

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Abstract: While drug resistant mutations in HIV-1 are largely credited to its error prone HIV-1 RT, the time point in the infection cycle that these mutations can arise and if they appear spontaneously without selection pressures both remained enigmatic. Many HIV-1 RT mutational in vitro studies utilized reporter genes (LacZ) as a template to investigate these questions, thereby not accounting for the possible contribution of viral codon usage. To address this gap, we investigated HIV-1 RT mutation rates and biases on its own Gag, protease, and RT p66 genes in an in vitro selection pressure free system. We found rare clinical mutations with a general avoidance of crucial functional sites in the background mutations rates for Gag, protease, and RT p66 at 4.71×10^{-5}, 6.03×10^{-5}, and 7.09×10^{-5} mutations/bp, respectively. Gag and p66 genes showed a large number of 'A to G' mutations. Comparisons with silently mutated p66 sequences showed an increase in mutation rates ($1.8^{0} \times 10^{-4}$ mutations/bp) and that 'A to G' mutations occurred in regions reminiscent of ADAR n[illegible] an avoid[illegible]

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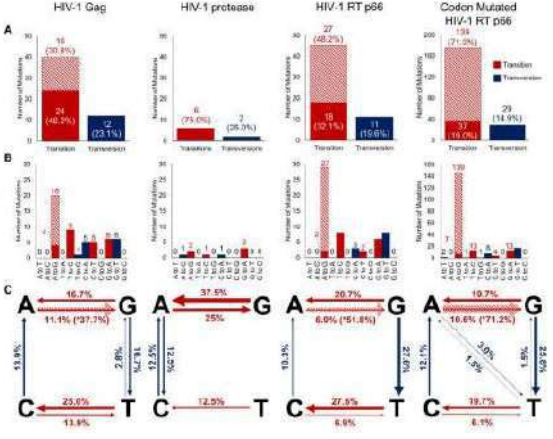
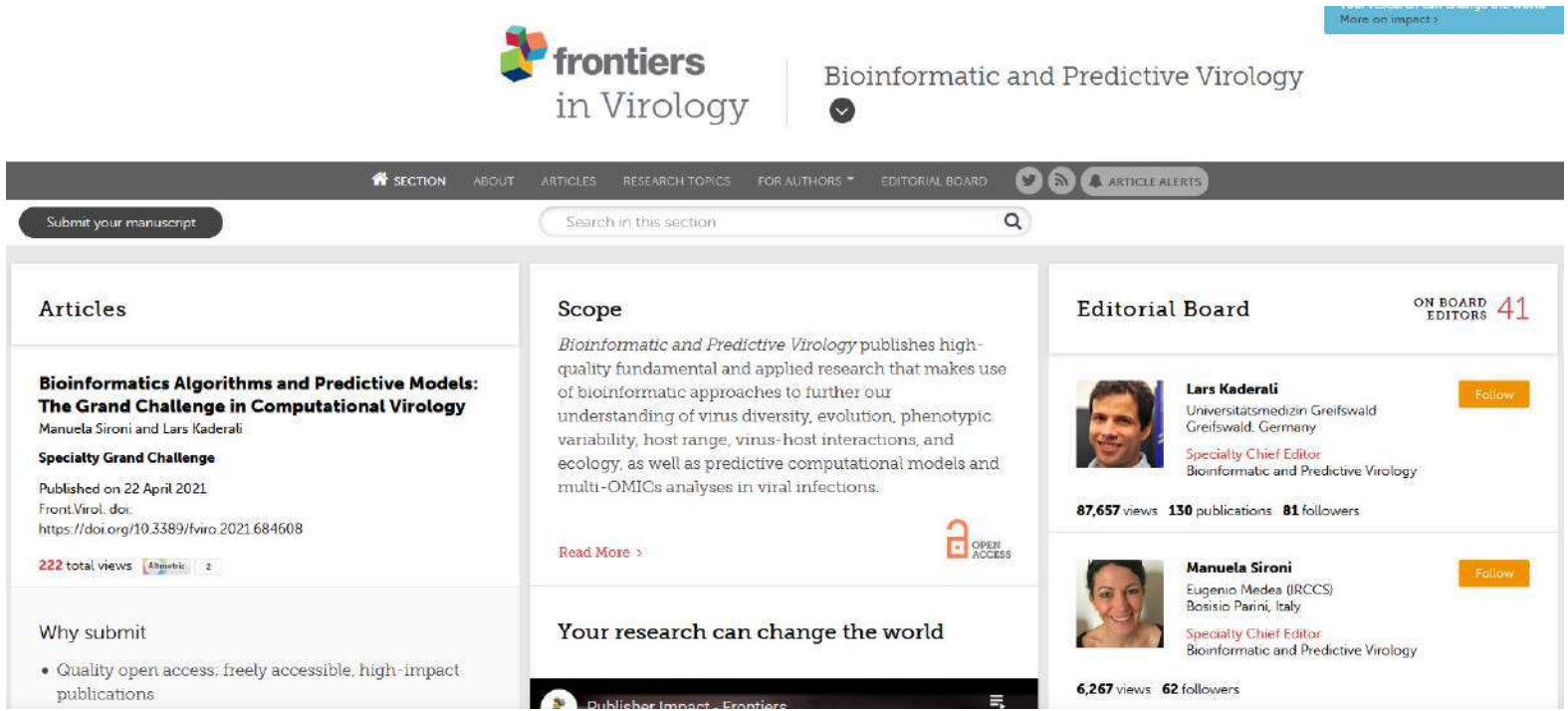
Citation: Yeo, J.Y.; Koh, D.W.-S.; Yap, P.; Goh, G.-R.; Can, S.K.-E. Spontaneous Mutations in HIV-1 Gag,

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