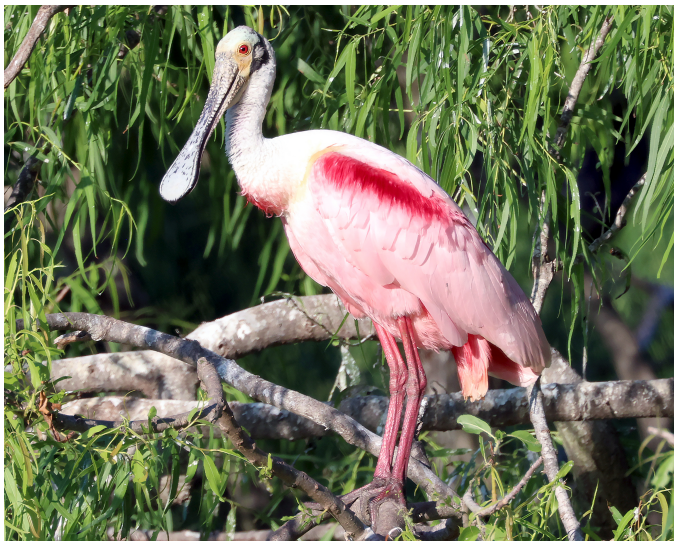



Alkanes
Alkenes
Alkynes
Haloalkanes
Vicinal dihaloalkanes
Ketones and Aldehydes
Carboxylic Acids
Alcohols
Where Electrons Are
Mechanisms
Roadmaps
Stereochemistry
Regiochemistry
ROTD
NIRRS
Motive
Opportunity
Carbocation
Radical
Pi-ways
Golden Rules
Make a Bond
Break a Bond
Add a Proton
Take a Proton
Nucleophiles and Electrophiles
Charge Delocalization
Hyperconjugation
Steric strain
Angle and Torsional Strain
Epoxides
Vicinal Diols
Radical Chain
SN2 vs. E2
SN1 and E1
Anti-periplanar
Markovnikov
Zaitsev
Alkenes
Alcohols
Epoxides
Aldehyes and Ketones
Carboxylic Acid Derivatives
Benzene Derivatives
Haloalkanes
Amines
Where Electrons Are
Mechanisms
Key Recognition Elements (KRE)
Stereochemistry
Regiochemistry
ROTD
Roadmaps
Motive
Opportunity
Enolate Ion
Arenium Ion
Pi-ways
Golden Rules
Make a Bond
Break a Bond
Add a Proton
Take a Proton
Nucleophiles and Electrophiles
Charge Delocalization
Conjugation
Electron Donating
Electron Withdrawing
Oxidation
Michael Reaction
Robinson Annulation
Good,Bad,Ugly Groups
Grignard Reagents
Gilman Reagents
Wittig Reagents
Mr. Bill Rxn

Background on the HIV virus → AIDS

1) HIV is a retrovirus → single strand of RNA inside a protein coat → codes for 19 proteins

2) HIV infects cells of the immune system → HIV binds to specific receptors on these cells

3) Once inside the cell the RNA is reverse transcribed to DNA by a viral enzyme.
"Reverse transcriptase"

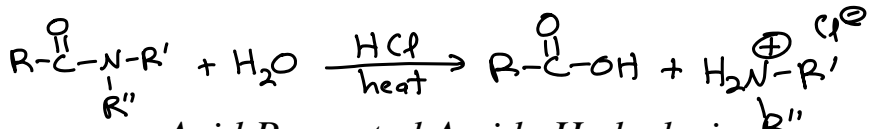
4) The DNA is integrated into the the host genome by another viral enzyme.
"Integrase"

→ The viral DNA remains inactive for some time within the DNA genome.

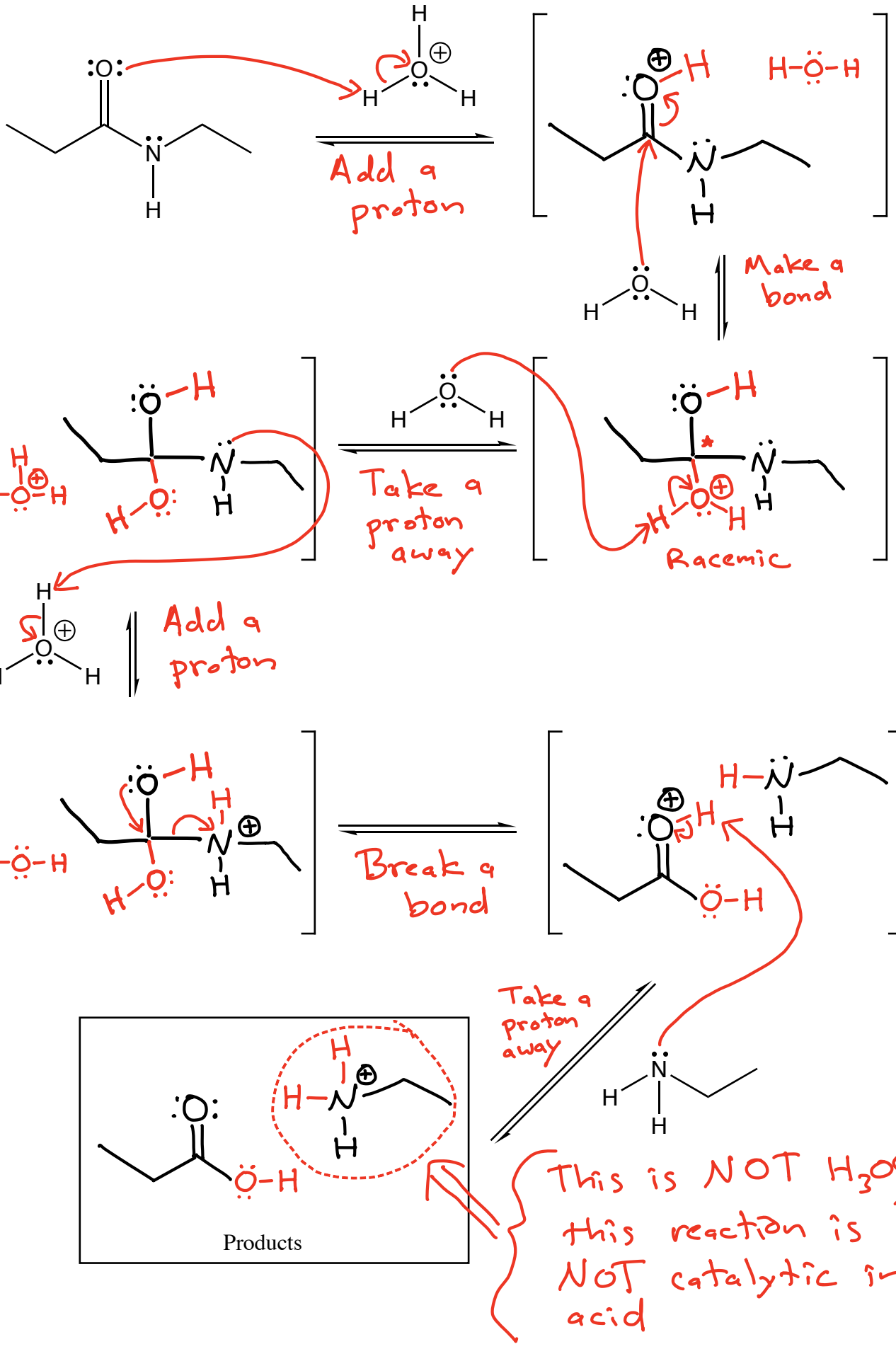
5) After an unknown signal, the viral DNA becomes active and produces a single long mRNA, that produces a very long HIV single protein. → called a polyprotein

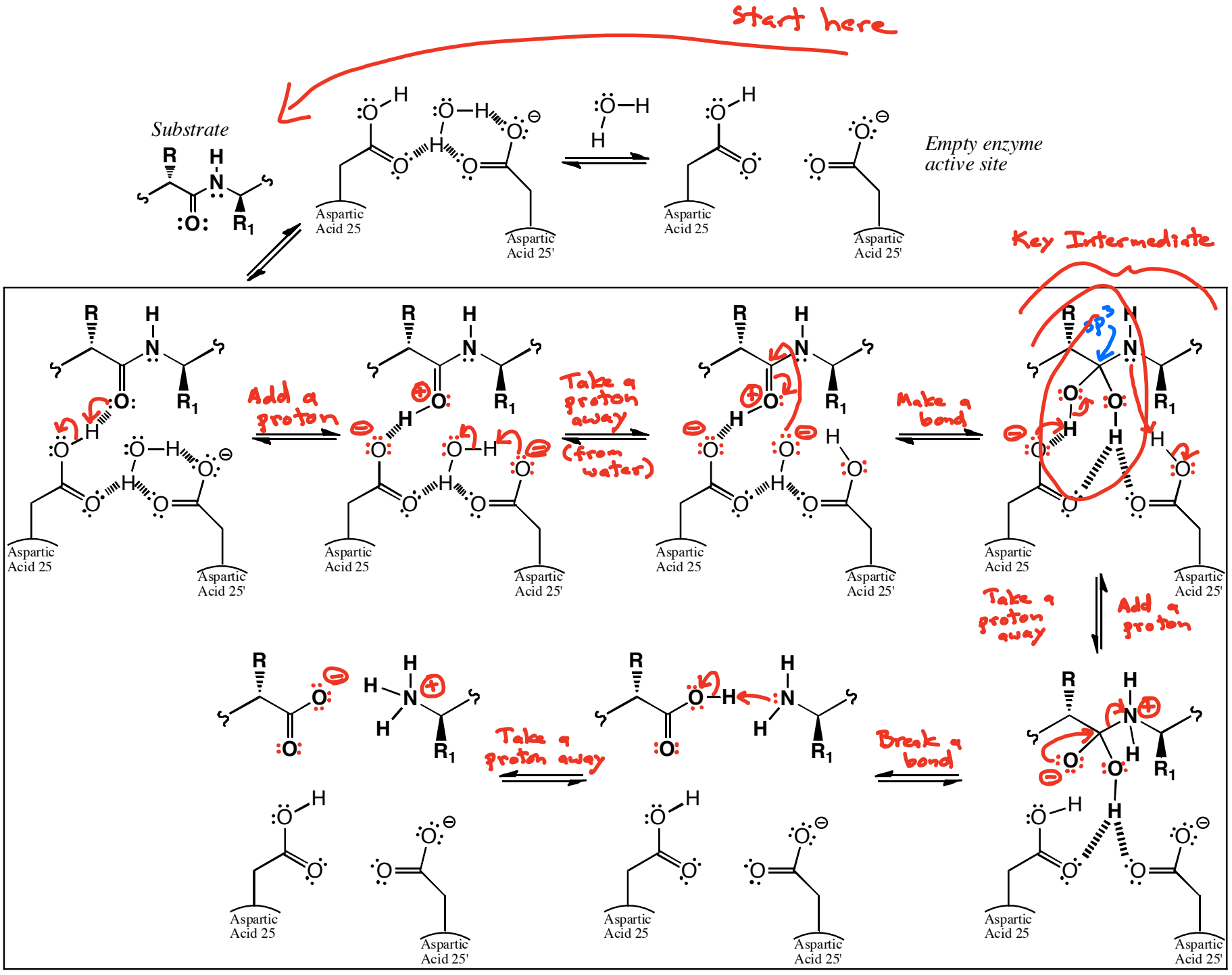
6) The HIV polyprotein is cleaved into individual proteins by another viral enzyme called the AIDS protease → cleaves amide bonds at the correct sequences. → has two carboxylic acids (Asp) at the correct location to cleave the amide bond. → called an aspartyl protease because of the two key carboxylic acid groups on aspartic acid amino acids (Asp).

Enzymes → catalyze reactions by having an active site that places acids, bases nucleophiles and sometimes metal atoms in exactly the correct 3-d space to make the reaction happen → the active sites also lower the energy of reactions by stabilizing high energy intermediates



Acid Promoted Amide Hydrolysis




Start here
Substrate
Aspartic Acid 25
Aspartic Acid 25'
Empty enzyme active site
Key Intermediate
Add a proton
Take a proton away (from water)
Make a bond
Take a proton away
Add a proton
Take a proton away
Break a bond
sp3

PERSPECTIVE

OBC
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HIV-1 protease: mechanism and drug discovery

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1 Introduction

It has now been two decades since acquired immunodeficiency syndrome (AIDS) was first reported by the US Center for Diseases Control (CDC). A few years later, it was found that a retrovirus called human immunodeficiency virus (HIV) is the causative agent in AIDS.[1] In a short time, AIDS increased to epidemic proportions throughout the world, affecting more than 40 million people today and killing so far more than 22 million (UNAIDS, 2001).

Since the outbreak of the AIDS epidemic, tremendous efforts have been directed towards development of antiretroviral therapies that target HIV type 1 in particular (HIV-1). The identification of the HIV retrovirus and the accumulated knowledge about the role of the different elements in its life cycle led researchers around the world to develop inhibitors that target different steps in the life cycle of the virus. One of these targets is HIV-1 protease (HIV PR), an essential enzyme needed in the proper assembly and maturation of infectious virions. Understanding the chemical mechanism of this enzyme has been a basic requirement in the development of efficient inhibitors. In this review, we summarize studies conducted in the last two decades on the mechanism of HIV PR and the impact of their conclusions on the drug discovery processes.

2 The life cycle of HIV

HIV belongs to the class of viruses called retroviruses, which carry genetic information in the form of RNA. HIV infects T cells that carry the CD4 antigen on their surface. The infection of the virus requires fusion of the viral and cellular membranes, a process that is mediated by the viral envelope glycoprotein (gp120, gp41) and receptors (CD4 and coreceptors, such as CCR5 or CXCR4) on the target cell. As the virus enters a cell, its RNA is reverse-transcribed to DNA by a virally encoded enzyme, the reverse transcriptase (RT). The viral DNA enters the cell nucleus, where it is integrated into the genetic material of the cell by a second virally encoded enzyme, the integrase. Activation of the host cell results in the transcription of the viral DNA into messenger RNA, which is then translated into viral proteins. HIV protease, the third virally encoded enzyme, is required in this step to cleave a viral polyprotein precursor into individual mature proteins. The viral RNA and viral proteins assemble at the cell surface into new virions, which then bud from the cell and are released to infect another cell. The extensive cell damage from the destruction of the host's genetic system to the budding and release of virions leads to the death of the infected cells.

3 HIV protease

3.1 HIV protease: a logical target for AIDS therapy

Unless the HIV life cycle is interrupted by specific treatment, the virus infection spreads rapidly throughout the body, which results in the weakness and destruction of the body's immune system. From the analysis of the HIV life cycle, one could conclude that there are several steps that might be interfered with, thus stopping the replication of the virus. For example, there are several commercially available drugs that inhibit the enzyme reverse transcriptase (RT). The first class of RT inhibitors is the nucleoside analogs such as AZT, ddI, ddC and d4T. These dideoxy compounds lack the 3′-hydroxy, causing DNA chain termination when they are incorporated into the growing DNA strand. The second class of inhibitors is the non-nucleoside inhibitors (NNIs); these inhibitors are known to bind in a pocket away from the polymerase active site, and are believed to cause a conformational change of the enzyme active site, and thus inhibit its action. Currently, there are three available non-nucleoside reverse transcriptase inhibitors (nevirapine, delavirdine, and efavirenz) for the treatment of AIDS.

Another critical step in the life cycle of HIV is the proteolytic cleavage of the polypeptide precursors into mature enzymes and structural proteins catalyzed by HIV PR. It has been shown that budded immature viral particles that contain catalytically inactive protease cannot undergo maturation to an infective form.[2] The necessity of this enzyme in the virus life cycle makes it a promising target for therapy of the HIV infection.[3]

3.2 Structure of HIV protease

Navia *et al.* from Merck laboratories were the first group to obtain a crystal structure of HIV PR;[4] a more accurate structure was reported subsequently by Kent and coworker.[5] HIV PR is a 99 amino acid aspartyl protease which functions as a homodimer with only one active site which is C_2-symmetric in the free form. More than 140 structures of the HIV-1 PR, its mutants and enzymes complexed with various inhibitors have been reported so far. A database dedicated to providing structural information about HIV PR has been created at the National Cancer Institute (http://www-fbsc.ncifcrf.gov/HIVdb/). The enzyme homodimer complexed with TL-3[6] is shown in Fig. 1 (PDB ID: 3TLH). Each monomer contains an extended β-sheet region (a glycine-rich loop) known as the flap, that constitutes in part the substrate-binding site and plays an important role in substrate binding, and one of the two essential aspartyl residues, Asp-25 and Asp-25′ which lie on the bottom of the cavity. The substrate binds in its extended conformation, in which its interactions with the different amino

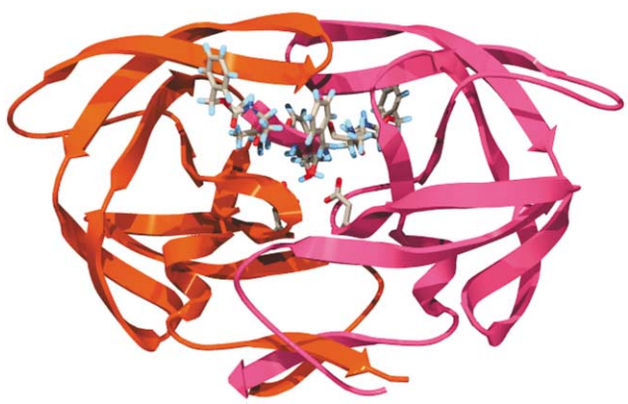


Fig. 1 Structure of HIV PR complexed with TL-3 (PDB: 3TLH).

DOI: 10.1039/b208248a

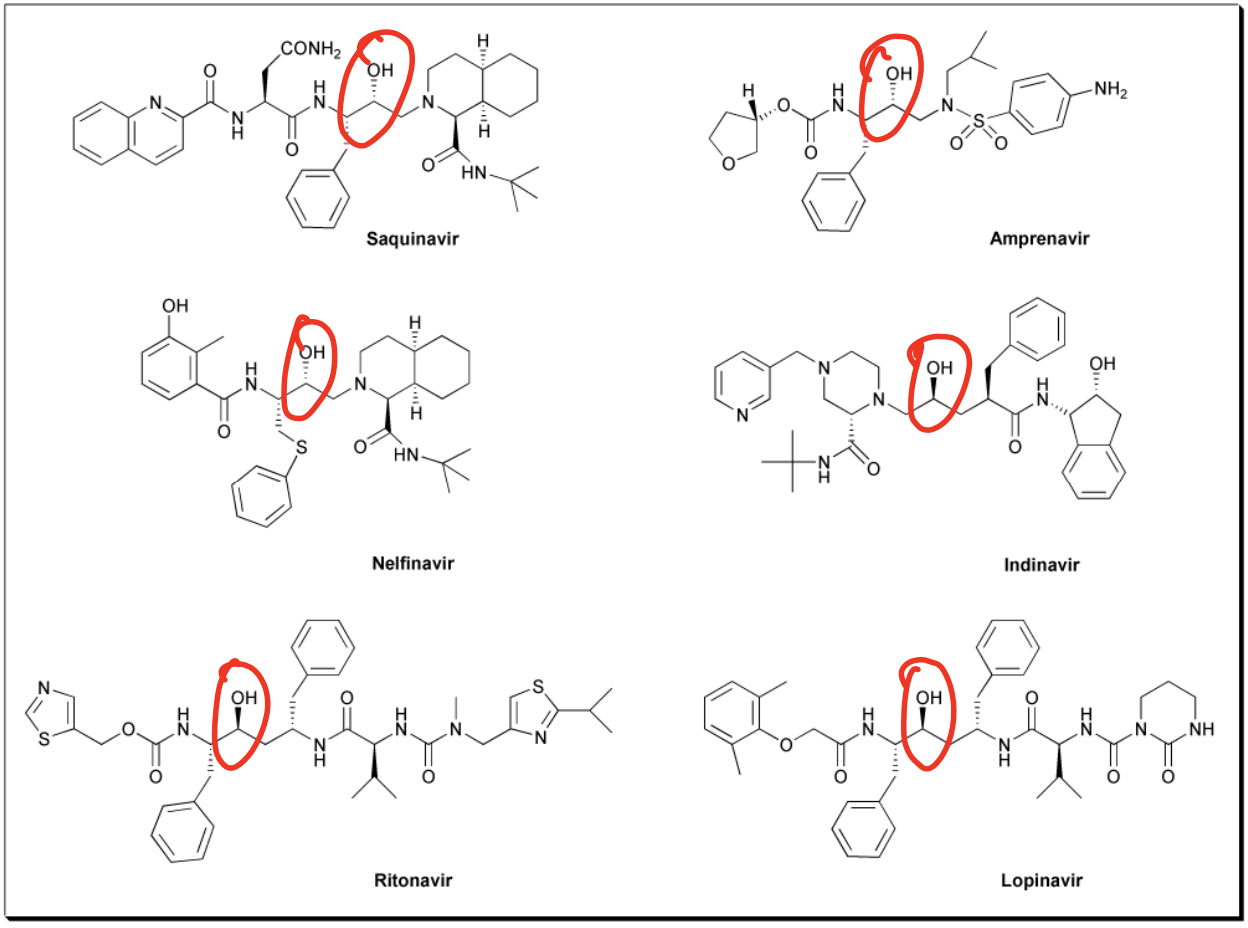
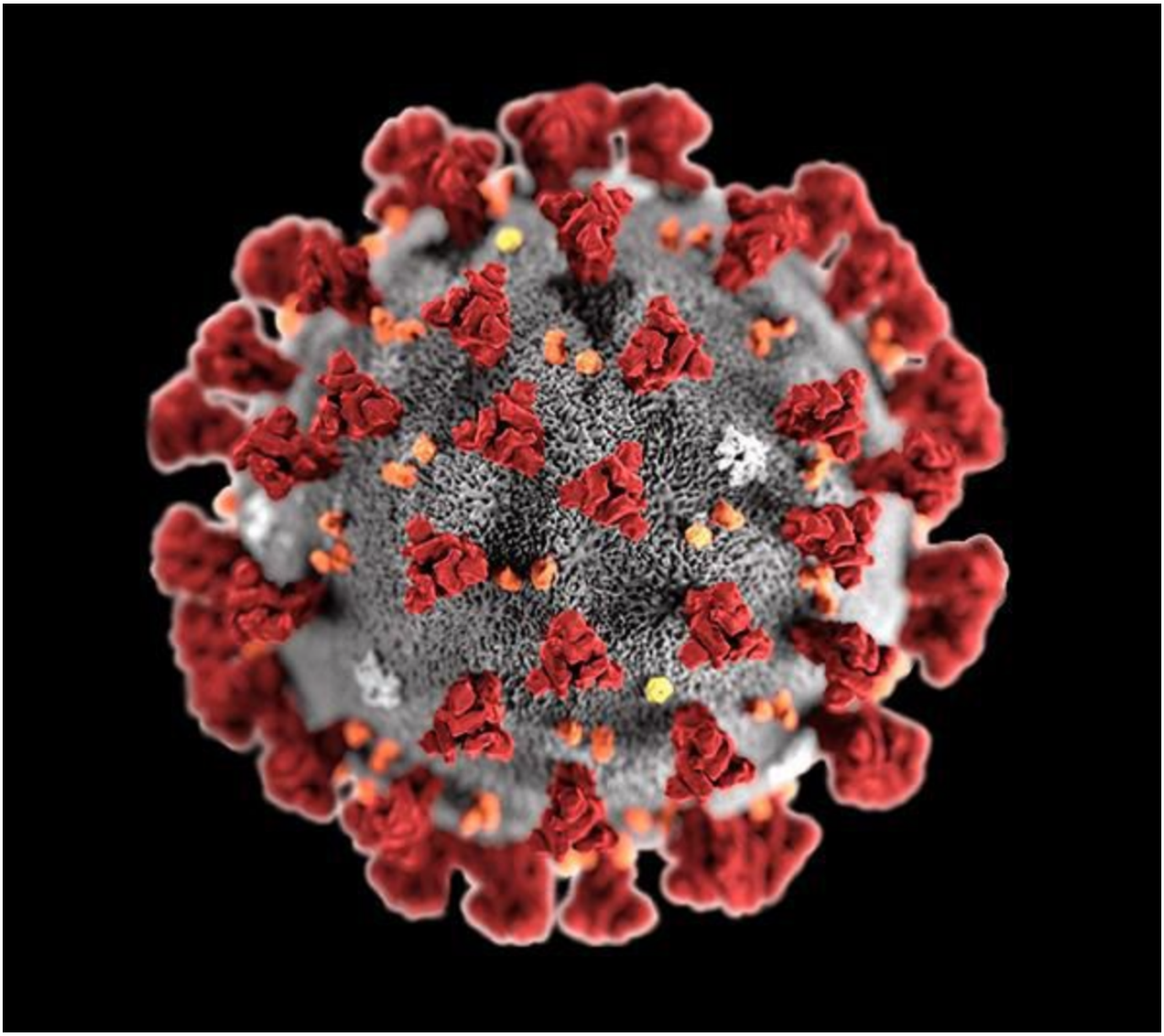


Fig. 10 FDA approved HIV-1 protease inhibitors.



Structure-based design of prefusion-stabilized SARS-CoV-2 spikes

Ching-Lin Hsieh[1], Jory A. Goldsmith[1], Jeffrey M. Schaub[1], Andrea M. DiVenere[2], Hung-Che Kuo[1], Kamyab Javanmardi[1], Kevin C. Le[2], Daniel Wrapp[1], Alison G. Lee[1], Yutong Liu[2], Chia-Wei Chou[1], Patrick O. Byrne[1], Christy K. Hjorth[1], Nicole V. Johnson[1], John Ludes-Meyers[1], Annalee W. Nguyen[2], Juyeon Park[1], Nianshuang Wang[1], Dzifa Amengor[1], Jason J. Lavinder[1,2], Gregory C. Ippolito[1,3], Jennifer A. Maynard[2]*, Ilya J. Finkelstein[1,4]*, Jason S. McLellan[1]*

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The COVID-19 pandemic has led to accelerated efforts to develop therapeutics and vaccines. A key target of these efforts is the spike (S) protein, which is metastable and difficult to produce recombinantly. Here, we characterized 100 structure-guided spike designs and identified 26 individual substitutions that increased protein yields and stability. Testing combinations of beneficial substitutions resulted in the identification of HexaPro, a variant with six beneficial proline substitutions exhibiting ~10-fold higher expression than its parental construct and the ability to withstand heat stress, storage at room temperature, and three freeze-thaw cycles. A 3.2 Å-resolution cryo-EM structure of HexaPro confirmed that it retains the prefusion spike conformation. High-yield production of a stabilized prefusion spike protein will accelerate the development of vaccines and serological diagnostics for SARS-CoV-2.

Mol Ther. 2008 November ; 16(11): 1833–1840. doi:10.1038/mt.2008.200.

Incorporation of Pseudouridine Into mRNA Yields Superior Nonimmunogenic Vector With Increased Translational Capacity and Biological Stability

Katalin Karikó[1], **Hiromi Muramatsu**[1], **Frank A Welsh**[1], **János Ludwig**[2], **Hiroki Kato**[3], **Shizuo Akira**[3], and **Drew Weissman**[4]

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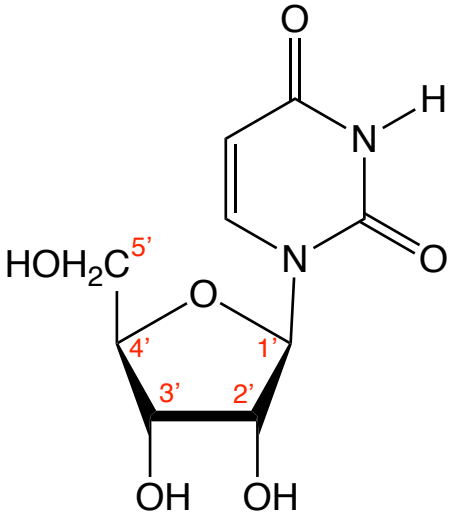
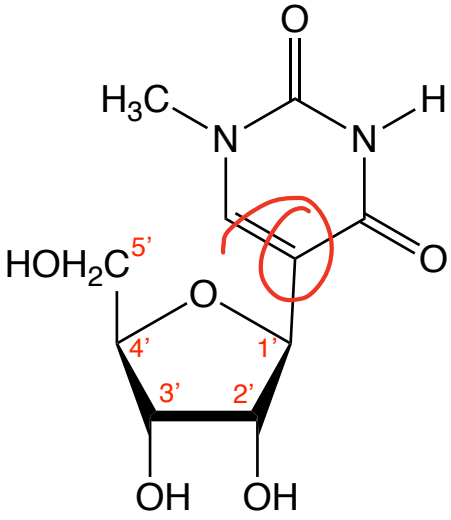
[4]Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Abstract

In vitro–transcribed mRNAs encoding physiologically important proteins have considerable potential for therapeutic applications. However, in its present form, mRNA is unfeasible for clinical use because of its labile and immunogenic nature. Here, we investigated whether incorporation of naturally modified nucleotides into transcripts would confer enhanced biological properties to mRNA. We found that mRNAs containing pseudouridines have a higher translational capacity than unmodified mRNAs when tested in mammalian cells and lysates or administered intravenously into mice at 0.015–0.15 mg/kg doses. The delivered mRNA and the encoded protein could be detected in the spleen at 1, 4, and 24 hours after the injection, where both products were at significantly higher levels when pseudouridine-containing mRNA was administered. Even at higher doses, only the unmodified mRNA was immunogenic, inducing high serum levels of interferon-α (IFN-α). These findings indicate that nucleoside modification is an effective approach to enhance stability and translational capacity of mRNA while diminishing its immunogenicity *in vivo*. Improved properties conferred by pseudouridine make such mRNA a promising tool for both gene replacement and vaccination.



Uridine



N1-methylpseudouridine
(m1Ψ)

Nobel Prize in Physiology or Medicine 2023

Katalin Karikó

Prize share: 1/2

Drew Weissman

Prize share: 1/2

Amy Rhoden Smith

Careers in Chemistry

Amy Rhoden Smith, PhD works at Precision BioSciences, a gene editing therapeutics company. As a program development leader, Dr. Rhoden Smith works with multiple teams to lead cell and gene editing therapy programs through preclinical and early clinical development. She loves working in biotechs and startups, where she can think about how to use cutting-edge science to bring meaningful therapies to patients. Dr. Rhoden Smith earned her BS in chemistry at the College of Charleston. She received her PhD in organic chemistry from the University of Texas at Austin.

Dr. Rhoden Smith has always been interested in applying her chemical knowledge to understand biological problems, so she started her career in biotechnology by joining Moderna Therapeutics. Her team used chemistry to create novel therapeutic mRNA conjugates for improved mRNA in vivo half-life and protein expression. She then moved to Intellia Therapeutics, where she led a team focused on generating Cas9 mRNA and synthetic guide RNAs for in vivo gene editing therapeutic applications. After working on projects that were discovery-based, she moved to Precision BioSciences, where she focuses on bringing products into the clinic.

Dr. Rhoden Smith says that organic chemistry gave her an understanding of how molecules interact with each other, which applies not only to small molecules, but also much larger ones like proteins, nucleic acids, and even cells. Just as importantly, it also taught her the value of problem-solving and gave her a passion for understanding complex problems, which she uses every day.

Molecular Therapy
Original Article

A Novel Amino Lipid Series for mRNA Delivery: Improved Endosomal Escape and Sustained Pharmacology and Safety in Non-human Primates

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The success of mRNA-based therapies depends on the availability of a safe and efficient delivery vehicle. Lipid nanoparticles have been identified as a viable option. However, there are concerns whether an acceptable tolerability profile for chronic dosing can be achieved. The efficiency and tolerability of lipid nanoparticles has been attributed to the amino lipid. Therefore, we developed a new series of amino lipids that address this concern. Clear structure-activity relationships were developed that resulted in a new amino lipid that affords efficient mRNA delivery in rodent and primate models with optimal pharmacokinetics. A 1-month toxicology evaluation in rat and non-human primate demonstrated no adverse events with the new lipid nanoparticle system. Mechanistic studies demonstrate that the improved efficiency can be attributed to increased endosomal escape. This effort has resulted in the first example of the ability to safely repeat dose mRNA-containing lipid nanoparticles in non-human primate at therapeutically relevant levels.

INTRODUCTION

mRNA-based therapies have the potential to revolutionize the way we treat diseases. The surging interest in mRNA as a drug modality stems from the potential to deliver transmembrane and intracellular proteins, targets that standard biologics are unable to access due to their inability to cross the cell membrane.[1] One major challenge to making mRNA-based therapies a reality is the identification of an optimal delivery vehicle. Due to its large size, chemical instability, and potential immunogenicity, mRNA requires a delivery vehicle that can offer protection from endo- and exo-nucleases, as well as shield the cargo from immune sentinels. Lipid nanoparticles (LNPs) have been identified as a leading option in this regard.[2] Moderna Therapeutics has recently validated this approach by demonstrating safe and effective delivery of an mRNA-based vaccine formulated in LNPs.[3]

Key performance criteria for an LNP delivery system are to maximize cellular uptake and enable efficient release of mRNA from the endosome. At the same time, the LNP must provide a stable drug product and be able to be dosed safely at therapeutically relevant levels. LNPs are multi-component systems that typically consist of an amino lipid, phospholipid, cholesterol, and a PEG-lipid.[2] Each component is required for aspects of efficient delivery of the nucleic acid cargo and stability of the particle. The key component thought to drive cellular uptake, endosomal escape, and tolerability is the amino lipid. Cholesterol and the PEG-lipid contribute to the stability of the drug product both *in vivo* and on the shelf, while the phospholipid provides additional fusogenicity to the LNP, thus helping to drive endosomal escape and rendering the nucleic acid bioavailable in the cytosol of cells.

Several amino lipid series have been developed for oligonucleotide delivery over the past couple of decades.[4] The literature highlights direct links between the structure of the amino lipid and the resultant delivery efficiency and tolerability of the LNP. The amino lipid MC3 (DLin-MC3-DMA) is the most clinically advanced oligonucleotide delivery system, as siRNA formulated in MC3-based LNPs has progressed to phase III for the treatment of transthyretin-mediated amyloidosis.[5,6] More recently, literature reports have demonstrated the effectiveness of MC3-based LNPs to deliver mRNA.[7] LNPs of this class are quickly opsonized by apolipoprotein E (ApoE) when delivered intravenously (i.v.), which enables cellular uptake into hepatocytes by the low-density lipoprotein receptor (LDLr).[8] Concerns remain that MC3's long tissue half-life could contribute to unfavorable side effects hindering its use for chronic therapies.[9] In addition, LNPs can induce activation of the immune system resulting in complement activation-related pseudoallergy (CARPA), an acute immunological response that can lead to anaphylactic-like shock.[10]

To unleash the potential of mRNA therapies for humans, we required a class of LNPs with increased delivery efficiency along with a metabolic and toxicity profile that would enable chronic dosing in humans.

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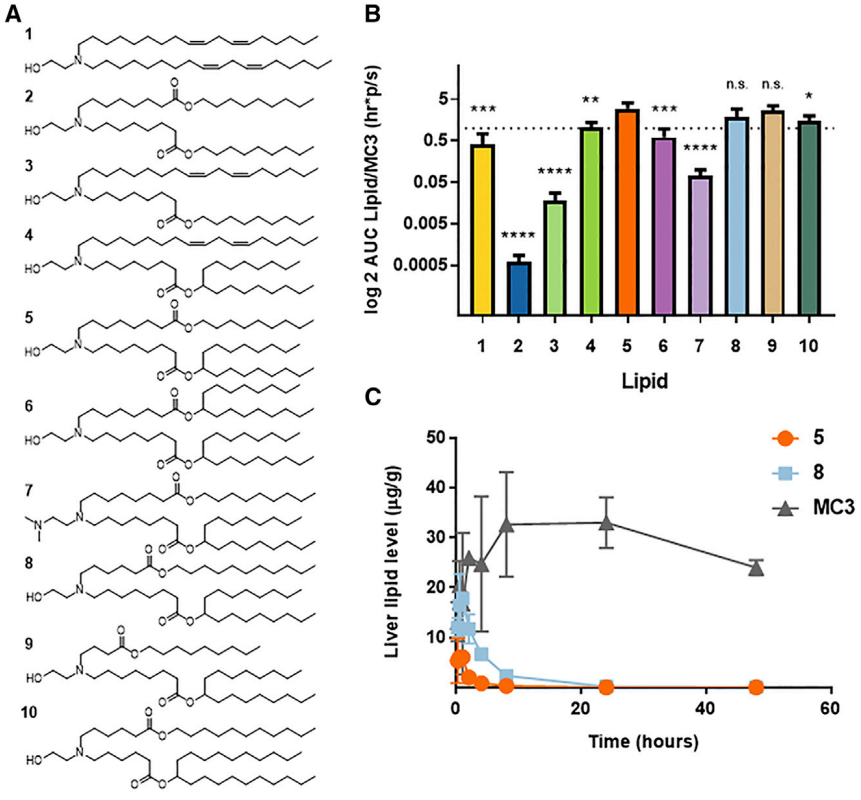

Figure 1. Optimization of Efficiency and Clearance of Amino Lipid

(A) Structures of amino lipids. (B) Whole-body luciferase bioluminescence AUC of novel LNPs versus MC3 LNPs, measured in CD-1 mice (n = 6 at 3 and 6 hr, n = 3 at 24 hr), 0.5 mg/kg dose firefly luciferase (ffLuc) mRNA, i.v. bolus, error bars indicate SD of the ratio of novel lipid AUC versus MC3 AUC. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001, n.s. = not statistically significant. (C) Parent amino lipid levels measured in liver tissue from Sprague-Dawley rats (n = 3 per time point), 0.2 mg/kg dose hEPO mRNA, mean ± SD, p < 0.05 for lipids 5 and 8 AUC relative to MC3.

We took a rational medicinal chemistry approach to amino lipid optimization aiming to identify structural motifs that provide chemical stability, optimal tissue clearance, and mRNA delivery efficiency. Our initial rodent screens led to the identification of a lead lipid with good delivery efficiency and pharmacokinetics. The lead LNP was profiled further in non-human primate for efficiency of delivery after single and repeat dosing. Finally, the optimized LNPs were evaluated in 1-month repeat dose toxicity studies in rat and non-human primate.

RESULTS

Initial screening of a broad chemical space identified ethanolamine as an amino lipid head group that could effectively drive mRNA encapsulation and provide LNPs with superior physiochemical properties. Combining the ethanolamine head group with di-linoleic lipid tails (lipid 1; Figure 1; Table 1) generated an LNP with high encapsulation of luciferase mRNA, small particle size, and low polydispersity index (PDI). The LNP with lipid 1 had a surface pK_a (apparent value for the particle) in the range that has been shown to be optimal for siRNA delivery.[11,12] To evaluate the efficiency of the new amino lipids, LNPs using the novel lipids were tested *in vivo* in mice using firefly luciferase mRNA as a reporter. An MC3 LNP was included as a control in each experiment, enabling us to compare LNPs from experiment to experiment. Measured luciferase activity also enabled us to determine protein bio-distribution. i.v. delivery of 0.5 mg/kg (mRNA dose level) of lipid 1-based LNPs to mice resulted in luciferase activity two-fold lower than an MC3 LNP control (Figure 1B). Whole-body imaging clearly demonstrated that the majority of protein expression was localized in the liver (Figure S1). We found that the lipid had similar clearance to MC3 from liver tissue with 66% of the original dose remaining in liver tissue of mice 24 hr post-dose (Table 1).

To improve tissue clearance, we introduced ester linkages in the lipid tails (lipids 2 and 3; Figure 1A), which are reported to trigger metabolism by esterases *in vivo*.[13] This has been shown to be a viable strategy to improve lipid clearance in a MC3-based lipid structure.[9] First, we established that the lipids were chemically stable by measuring ethanol stability at room temperature and 37°C (Table S1). We observed less than 1% change in purity for all lipids tested. LNPs formed with lipid 2 were significantly larger with a surface pK_a > 7 (Table 1). Removal of one ester (lipid 3) afforded LNPs with improved physiochemical characteristics and lower LNP surface pK_a. *In vivo*, neither lipid demonstrated efficient mRNA delivery (Figure 1B); however, we did observe rapid tissue clearance, with no lipid detected at 24 hr (Table 1).

Improvement in protein expression was observed when a secondary ester was introduced (lipid 4; Figures 1A and 1B). We observed equivalent expression to MC3 LNPs, but the clearance rate was slower than lipids 2 and 3 (67% lipid remaining; Table 1). Replacement of the linoleic tail with a primary ester-containing lipid tail (lipid 5; Figure 1A) provided increased expression (3-fold higher than MC3; Figure 1B) and optimal tissue clearance (no lipid detected at 24 hr; Table 1). To further increase expression an additional secondary ester was introduced (6), but this resulted in a lowering of the surface pK_a to 6.00 and lower luciferase activity. In addition, the lipid had a significantly slower tissue clearance with 68% remaining at 24 hr.

With an optimal lipid tail structure identified we re-visited the ethanolamine head group. Lipid 7 is one representative example (Figure 1A) where the alcohol functionality is replaced with a dimethylamine. This generated an LNP with comparable physiochemical properties, but complete loss of delivery efficiency (Figure 1B).

Structure-based design of prefusion-stabilized SARS-CoV-2 spikes

Ching-Lin Hsieh[1], Jory A. Goldsmith[1], Jeffrey M. Schaub[1], Andrea M. DiVenere[2], Hung-Che Kuo[1], Kamyab Javanmardi[1], Kevin C. Le[2], Daniel Wrapp[1], Alison G. Lee[1], Yutong Liu[2], Chia-Wei Chou[1], Patrick O. Byrne[1], Christy K. Hjorth[1], Nicole V. Johnson[1], John Ludes-Meyers[1], Annalee W. Nguyen[2], Juyeon Park[1], Nianshuang Wang[1], Dzifa Amengor[1], Jason J. Lavinder[1,2], Gregory C. Ippolito[1,3], Jennifer A. Maynard[2]*, Ilya J. Finkelstein[1,4]*, Jason S. McLellan[1]*

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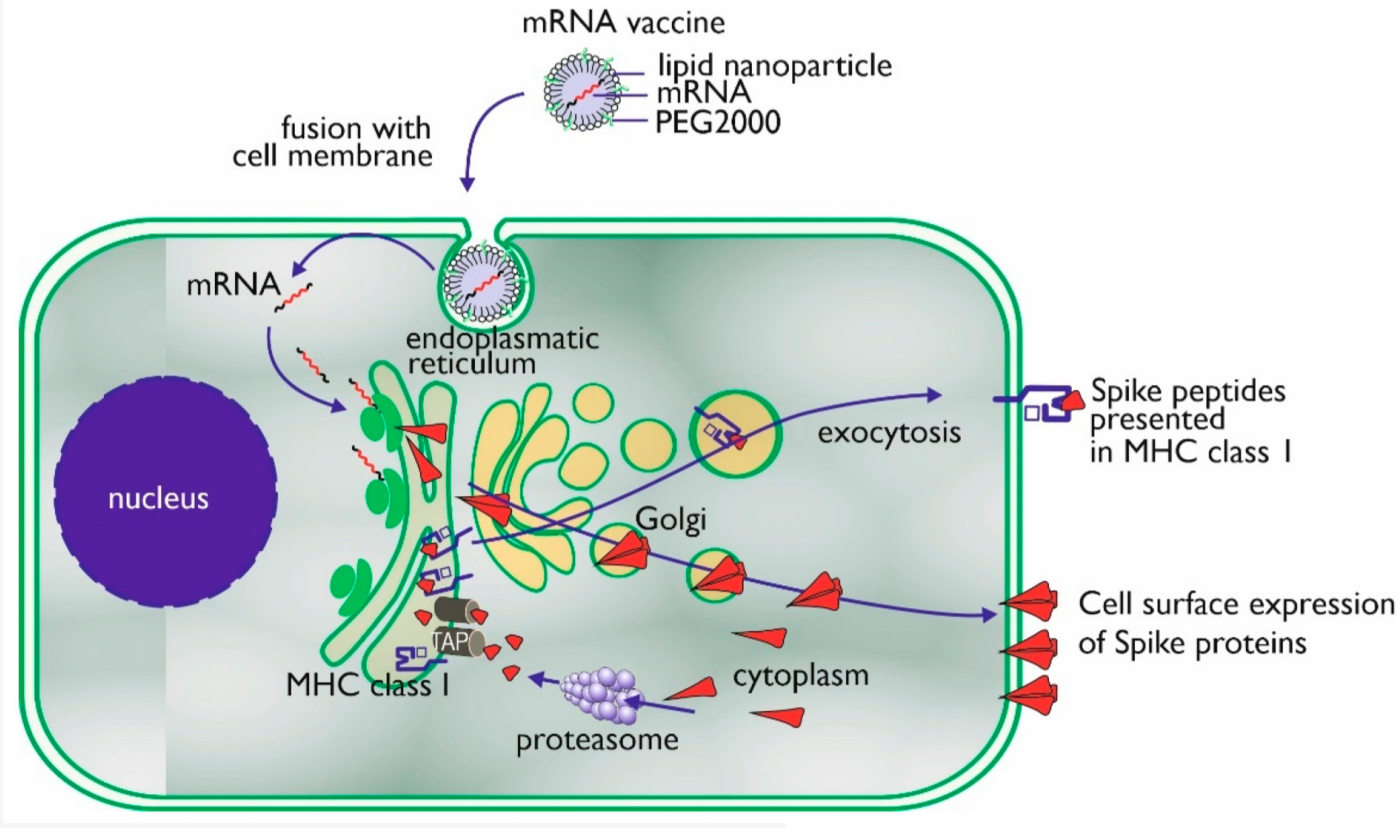
The COVID-19 pandemic has led to accelerated efforts to develop therapeutics and vaccines. A key target of these efforts is the spike (S) protein, which is metastable and difficult to produce recombinantly. Here, we characterized 100 structure-guided spike designs and identified 26 individual substitutions that increased protein yields and stability. Testing combinations of beneficial substitutions resulted in the identification of HexaPro, a variant with six beneficial proline substitutions exhibiting ~10-fold higher expression than its parental construct and the ability to withstand heat stress, storage at room temperature, and three freeze-thaw cycles. A 3.2 Å-resolution cryo-EM structure of HexaPro confirmed that it retains the prefusion spike conformation. High-yield production of a stabilized prefusion spike protein will accelerate the development of vaccines and serological diagnostics for SARS-CoV-2.



Vaccines **2021**, *9*(8), 848; **https://doi.org/10.3390/vaccines9080848**

New UT cases

The University of Texas said two people in its community, an unnamed student and the Dean of Undergraduate Studies Brent Iverson, had tested positive for the virus. It is unclear if the pair are included in Travis County's count of confirmed cases.

CORONAVIRUS

Prevalent, protective, and convergent IgG recognition of SARS-CoV-2 non-RBD spike epitopes

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The molecular composition and binding epitopes of the immunoglobulin G (IgG) antibodies that circulate in blood plasma after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are unknown. Proteomic deconvolution of the IgG repertoire to the spike glycoprotein in convalescent subjects revealed that the response is directed predominantly (>80%) against epitopes residing outside the receptor binding domain (RBD). In one subject, just four IgG lineages accounted for 93.5% of the response, including an amino (N)-terminal domain (NTD)–directed antibody that was protective against lethal viral challenge. Genetic, structural, and functional characterization of a multidonor class of "public" antibodies revealed an NTD epitope that is recurrently mutated among emerging SARS-CoV-2 variants of concern. These data show that "public" NTD-directed and other non-RBD plasma antibodies are prevalent and have implications for SARS-CoV-2 protection and antibody escape.

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CORONAVIRUS

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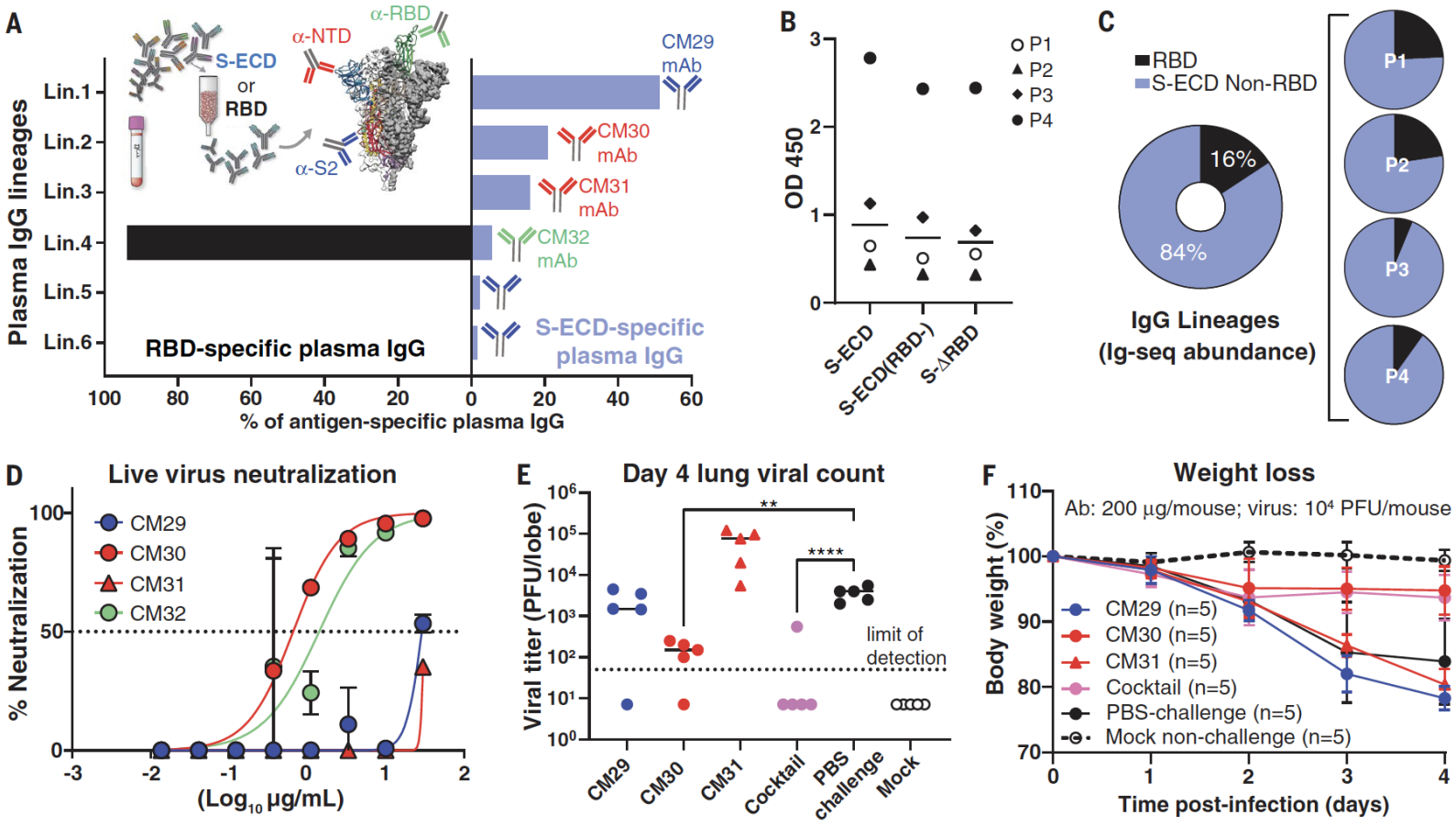

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Article

An Investigation of Nirmatrelvir (Paxlovid) Resistance in SARS-CoV-2 M^{pro}

Rasha M. Yaghi, Dennis C. Wylie, Collin L. Andrews, Olivia H. Dickert, Anjana Ram, and Brent L. Iverson*

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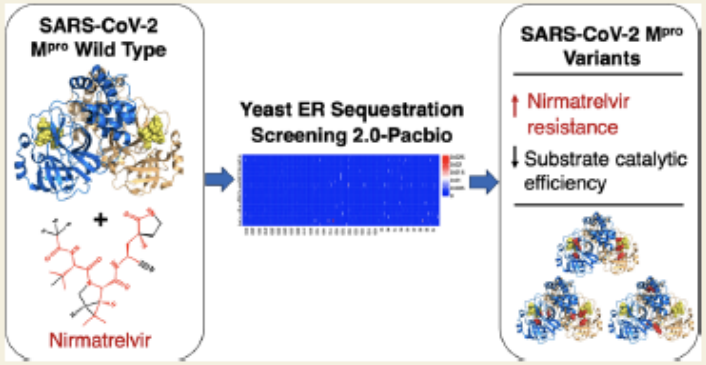
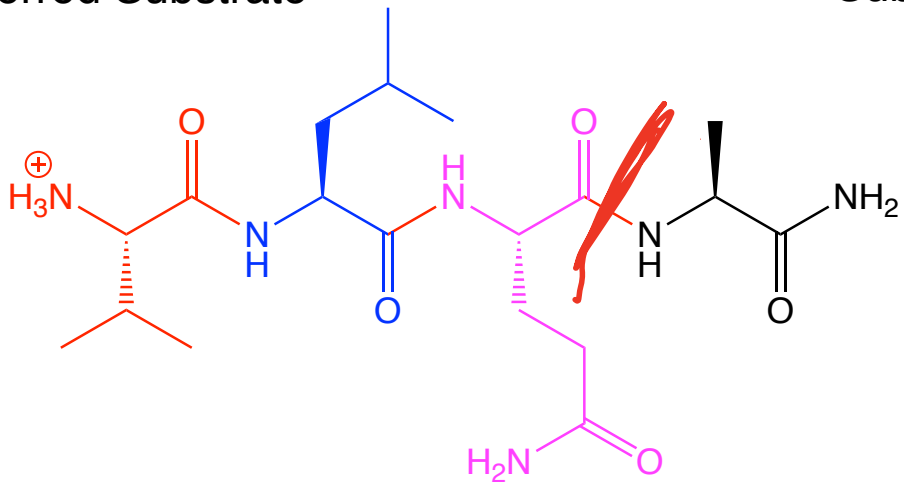
ABSTRACT: The high throughput YESS 2.0 platform was used to screen a large library of SARS-CoV-2 M^{pro} variants in the presence of nirmatrelvir. Of the 100 individual most prevalent mutations identified in the screen and reported here, the most common were E166V, L27V, N142S, A173V, and Y154N, along with their various combinations. *In vitro* analysis revealed that resistance to nirmatrelvir for these individual mutations, as well as all of the combinations we analyzed, was accompanied by decreased catalytic activity with the native substrate. Importantly, the mutations we identified have not appeared as significantly enriched in SARS-CoV-2 M^{pro} sequences isolated from COVID-19 patients following the introduction of nirmatrelvir. We also analyzed three of the most common SARS-CoV-2 M^{pro} mutations that have been seen in patients recently, and only a measured increase in nirmatrelvir resistance was seen when the more recently appearing A285V is added to both P132H and K90R. Taken together, our results predict that resistance to nirmatrelvir will be slower to develop than expected based on experience with other viral protease inhibitors, perhaps due in part to the close structural correspondence between nirmatrelvir and SARS-CoV-2 M^{pro}'s preferred substrates.

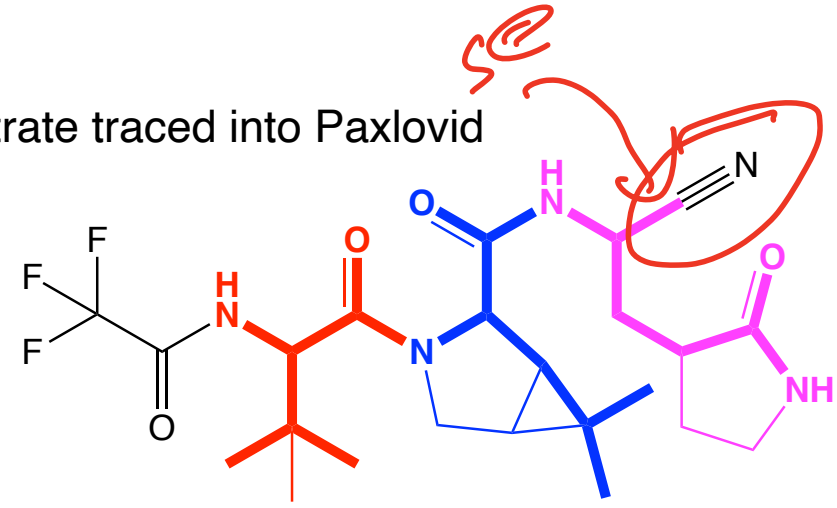


KEYWORDS: *protease, YESS, COVID-19, Paxlovid, nirmatrelvir resistance*

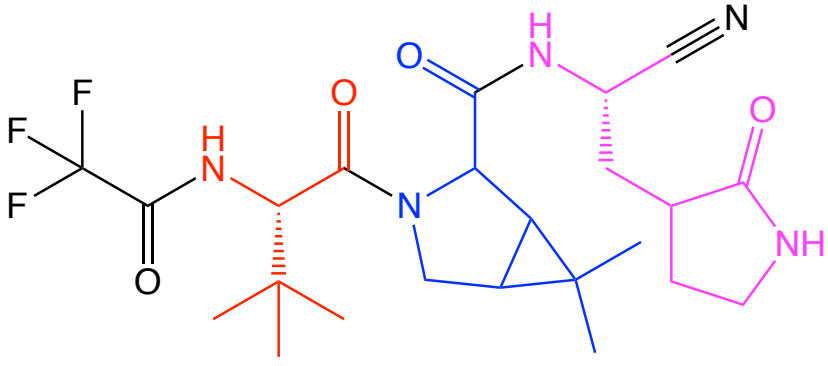
Preferred Substrate

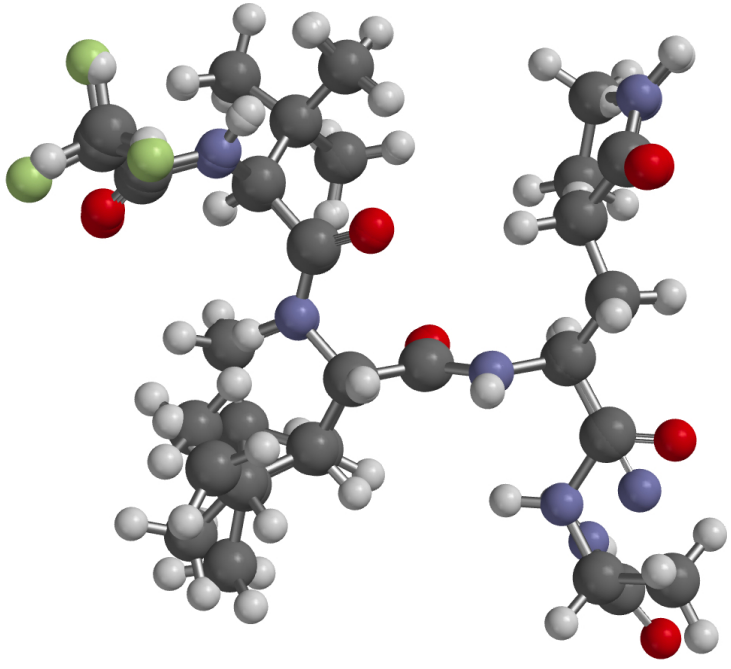


Substrate traced into Paxlovid



Paxlovid





<u>Organic Chemistry</u> is the study of carbon-containing molecules. This class has two points.

The first point of the class is to understand the organic chemistry of living systems. We will teach you how to think about and understand the most amazing molecules on the planet!!

You will learn how MRI scans work. 1/14/26

You will learn the basic principles of pharmaceutical science and how many drugs work. 1/21/26

You will learn about the special bond that holds carbohydrates such as glucose in six-membered rings, connects carbohydrate monomers together to make complex carbohydrate structures and is critical to DNA and RNA structure. 2/2/26

You will learn how soap is made from animal fat and how it works to keep us clean. 2/23/26

You will learn the important structural reason proteins, the most important molecular machines in our bodies, can support the chemistry of life. 2/16/26

You will learn how important antibiotics like penicillins work, including ones that make stable covalent bonds as part of their mode of action. 4/1/26

You will learn why carrots are orange and tomatoes are red. 3/25/26

You will learn the very cool reason that the DNA and RNA bases are entirely flat so they can stack in the double helix structure. 4/8/26

You will learn how energy drinks work. 4/22/26

You will learn even more about why fentanyl is such a devastating part of the opioid problem and how Naloxone is an antidote for a fentanyl overdose. 4/22/26

You will learn even more details about why Magic Johnson is still alive, decades after contracting HIV, and how the same strategy is being used to fight COVID. 4/27/26

You will learn about the surprising chemical reason the Pfizer and Moderna mRNA vaccines elicit strong immune responses. 4/27/26

The second point of organic chemistry is the synthesis of complex molecules from simpler ones by making and breaking specific bonds, especially carbon-carbon bonds.

You will learn how carbon-metal bonds lead to new carbon-carbon bonds. 1/21/26

You will learn how most reactions of carbonyl compounds involve only the four common mechanistic elements operating in only a few common patterns. 1/21/26

You will learn how, by simply adding a catalytic amount of base like HO^- to aldehydes or ketones, you can make new carbon-carbon bonds, giving complicated and useful products. 3/2/26

You will learn a reaction that can convert vinegar and vodka into a common solvent. 2/11/26 (Fischer esterification)
CH_3CO_2H CH_3CH_2OH $CH_3C(=O)OCH_2CH_3$

You will learn why molecules with six-membered rings and alternating double bonds are stable. 3/30/26

You will learn a reaction that can turn model airplane glue into a powerful explosive. 4/13/26

Most important, you will develop powerful critical thinking skills:

1. You will learn how to look at a molecule and accurately predict which atoms will react to make new bonds, and which bonds will break during reactions.
2. You will learn how to analyze a complex molecule's structure so that you can predict ways to make it via multiple reactions starting with less complex starting molecules.

"Organic Labville"

There must be a mistake,
What did I just make
Those aren't crystals, it looks more like oil.
Looks like another screw up,
Like the last one that blew up,
Uh oh now its beginning to boil.

Wasting my time again in my organic lab.
Looking for that last product I lost.
Some people say that my lab partners to blame,
But I know, its my T.A.'s fault.

Don't know the reason,
I always get C's in
My lab notebook it looks good to me.
I copy it from Suzy,
She's a real cutie,
Why she doesn't like me I haven't a clue.

Wasting my time again in my organic lab.
Looking for that last product I lost.
Some people say that my bad technique is to blame,
But I know, its my T.A.'s fault.

There's another fire in Welch,
AFD just can't squelch.
They said it wasn't safe so they sent us all home.
But there's chemicals in my blender
And I hope it will render,
That crystalline product I need to be done.

Wasting my time again in my organic lab.
Looking for that last product I lost.
Some people say that the professor is to blame,
But I know, its my T.A.'s fault.
Yes and Some people say that the professor is to blame,
But I know, its my T.A.'s fault.

Ring of Pi

Benzene is a funny thing
‘Cause it is a special ring
Hückel’s rules, they do apply
For a ring, a ring of pi

Electrons in a big old ring of pi
They go round, round, round.
And stability is high.
As we learn, learn, learn,
The ring of pi-i
The ring of pi.

The structure, it is sweet
When 4N and then 2 meet
Sp2, and flat required
Then the 2p’s, they are wired

Electrons in a big old ring of pi
They go round, round, round.
And stability is high,
As we learn, learn, learn,
The ring of pi-i
The ring of pi.

Electrons in a big old ring of pi
They go round, round, round.
And stability is high,
As we learn, learn, learn,
The ring of pi-i
The ring of pi.

Oh Lord, Make Me A Doctor With A Mercedes-Benz

Oh Lord, make me a doctor with a Mercedes-Benz
My friends are all prelaw, I must make amends.
Worked hard in organic, never thought it would end.
So Lord, make me a doctor, with a Mercedes-Benz.

Oh Lord, won't you give me an "A" on the test,
I have to show med-schools that I am the best.
Tried hard all semester, the TA says I'm a pest,
So Lord, won't you give me an "A" on the test.

Oh Lord, won't you give me a high MCAT score.
My friends all got 520's, I have to get more.
I went to Kaplan, oh man what a bore,
So Lord, won't you give me a high MCAT score.

Oh Lord, won't you get me into Johns Hopkins U.
Baylor would be nice, I'd like an interview
O.K. let's be serious, A&M will do.
So Lord, won't you get me into TAMU.

Oh Lord, make me a doctor with a Mercedes-Benz
My friends are all prelaw, I must make amends.
Worked hard in organic, never thought it would end.
So Lord, make me a doctor, with a Mercedes-Benz.

“Make it B”

On the final when I’m having trouble
Inspiration comes to me
I’m hearing words of wisdom
Make it B
And in my hour of darkness,
The answer is standing right in front of me,
Speaking words of wisdom
Make it B

Make it B, Make it B, Make it B, Make it B
Here are words of wisdom
Make it B

A tetrahedral intermediate
And a leaving group you see
This will be the answer, Make it B
No time to be that downhearted,
There is still a chance that you will see
With a leaving group, Make it B

Make it B, Make it B, Make it B, Make it B
This will be the answer,
Make it B

Make it B, Make it B, Make it B, Make it B
With a leaving group,
Make it B

Make it B, Make it B, Make it B, Make it B
Mechanism B,

Make it B

And when my mind is cloudy
There is still a light that shines on me,
Shinin until tomorrow, make it B
The Claisen is a great reaction
Chemists of the world agree
For Claisen its the answer
Make it B

Make it B, Make it B, Make it B, Make it B
With a leaving group,
Make it B

Make it B, Make it B, Make it B, Make it B
Mechanism B,
Make it B

We All Love Organic Chemistry

In the town where I was born,
Lived a man of chemistry.
And he told us of his life
In the organic laboratory.

Making molecules to fight disease
Coming up with their syntheses.
So we sit in 320N
Learning organic chemistry.

Refrain:
We all love organic chemistry
Synthetic chemistry
Molecules with "C"
We all love organic chemistry
Synthetic chemistry
Molecules with "C"

All our friends think we're a bore
Our grade point averages begin with 4.
But we await graduation day
To work in lab for meager pay.

But its OK, who else can say
They're curing cancer or fighting AIDS.
We hope that you in 320N
Respect organic chemistry

Refrain:
We all love organic chemistry
Synthetic chemistry
Molecules with "C"
We all love organic chemistry
Synthetic chemistry
Molecules with "C"