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Questions
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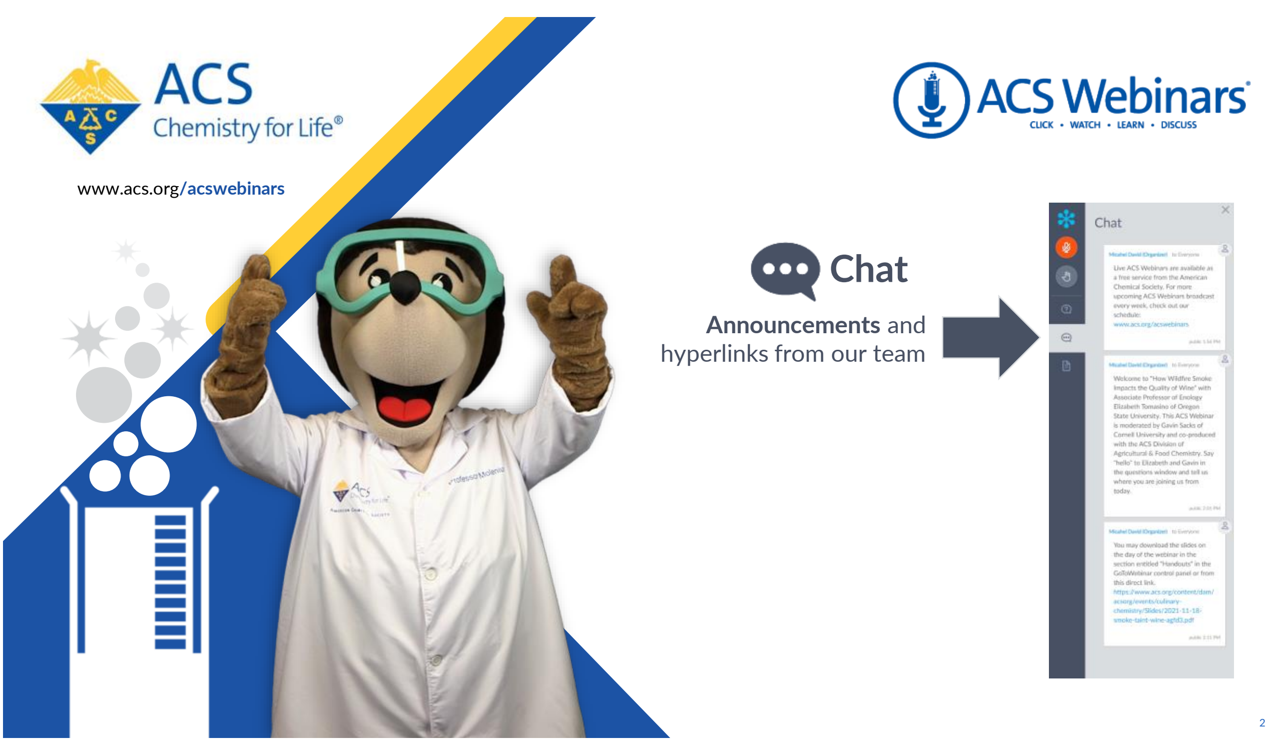
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2

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3

3

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ChemIDP is an Individual Development Plan designed specifically for graduate students and postdoctoral scholars in the chemical sciences. Through immersive, self-paced activities, users explore potential careers, determine specific skills needed for success, and develop plans to achieve professional goals. **ChemIDP** tracks user progress and input, providing tips and strategies to complete goals and guide career exploration.

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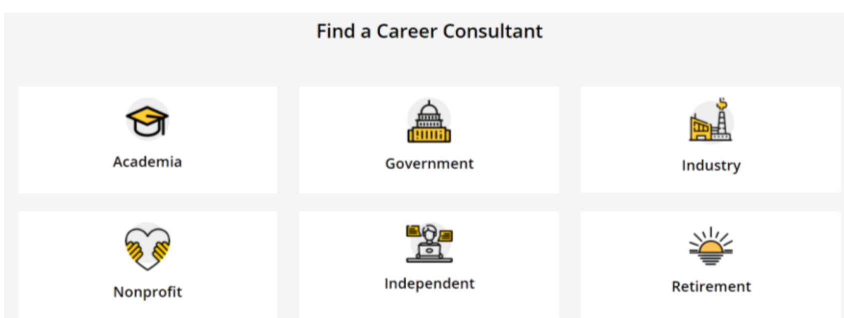
5

5

Career Consultant Directory



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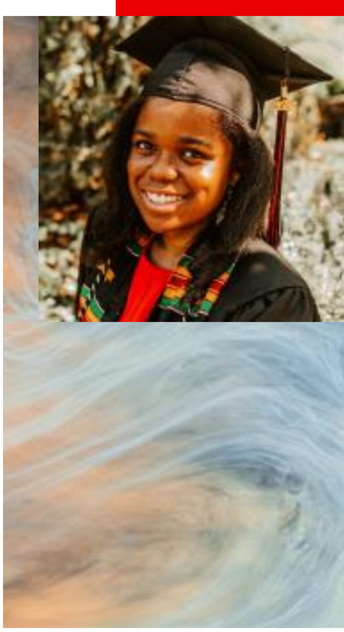

ACS Scholar Adunoluwa Obisesan

BS, Massachusetts Institute of Technology, June 2021
(Chemical-biological Engineering, Computer Science & Molecular Biology)

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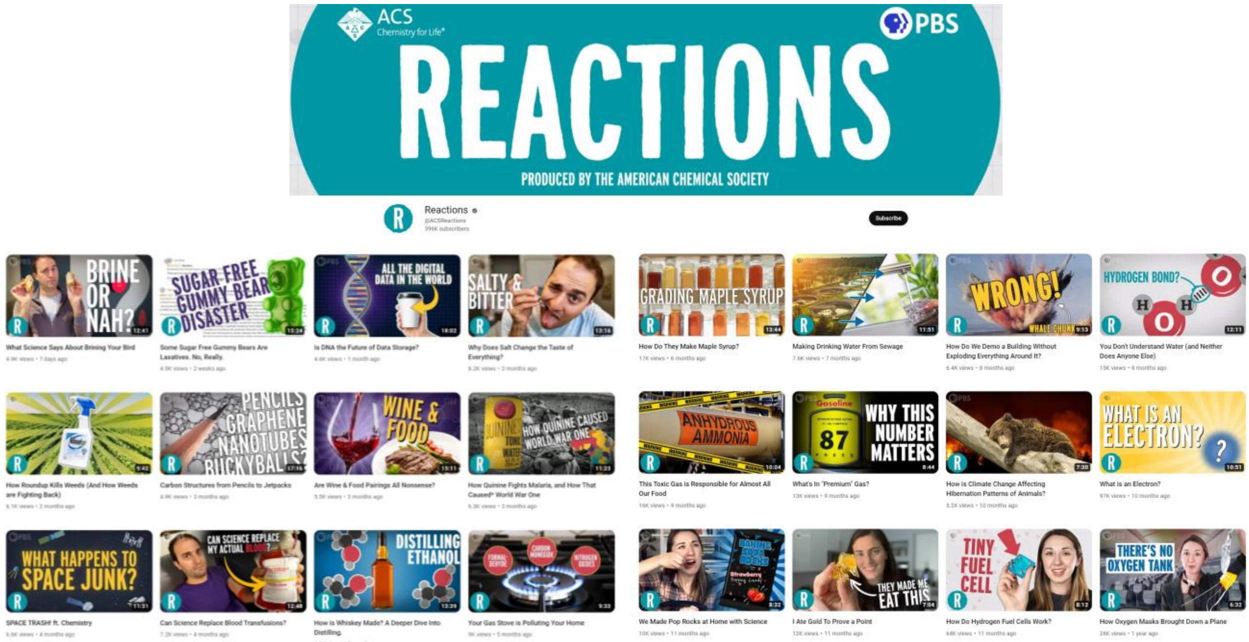

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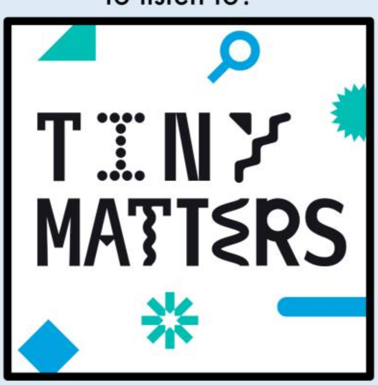

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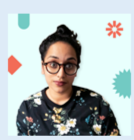
Sam Jones, PhD
Science Writer & Exec Producer



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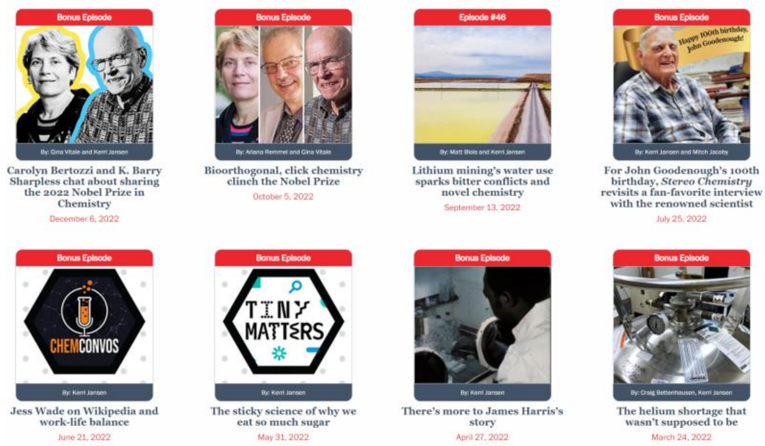

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Personal Career Consultations

Jim Tung

Marketing
Lacamas Laboratories

B.S., Biochemistry, University of Oregon
Ph.D., Organic Chemistry, University of Notre Dame

Jim Tung works at Lacamas Laboratories in Portland, OR, currently as a business development manager. He has been with Lacamas for 10 years, working on developing new chemical manufacturing projects. Before that, he was a senior research chemist at Obiter Research in Champaign, IL performing kilo-scale organic chemistry.

An Oregon native, Jim got his B.S. in biochemistry from the University of Oregon, his Ph.D. in organic chemistry from the University of Notre Dame, with postdoctoral experience at Pfizer's laboratories in La Jolla, CA. He is past chair of the Portland Section of the American Chemical Society and was 2019 general co-chair of NORM 2019. He has interests in process chemistry, labor economics, social media outreach and encouraging career exploration and development for younger chemists.

Ask me about:
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12

12

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13

13

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Advancing ACS' Core Value of Diversity, Equity, Inclusion and Respect

Resources

Inclusivity Style Guide
Designed to help staff and members use language and images that respect diversity in all its forms.

ACS Webinars on Diversity
Covering diversity and inclusion at the workplace

ACS Publications DEIR Hub
See what ACS Publications is doing for fostering inclusivity in scholarly publishing

ACS Volunteer and ACS Meetings Code of Conduct
Fostering a positive and welcoming environment for attendees, volunteers and staff.

C&EN Trailblazers
C&EN highlights scientists from different backgrounds who are making an impact in chemistry.

NEW! Download DEIR Educational Resources
Download this educational guide for additional recommendations on videos, articles, books, podcasts, and more on diversity, inclusion, and related topics.

Quick Guide: Inclusion Moments
Learn more about what Inclusion Moments are and see ideas to host them during your meetings.

Quick Guide: How to host inclusive in-person events
Recommendations and best practices to ensure that your events can accommodate everyone.

Diversity, Equity, Inclusion, and Respect

**Adapted from definitions from the Ford Foundation Center for Social Justice:

Equity**
Seeks to ensure fair treatment, equality of opportunity, and fairness in access to information and resources for all. We believe this is only possible in an environment built on respect and dignity. Equity requires the identification and elimination of barriers that have prevented the full participation of some groups.

Diversity**
The representation of varied identities and differences (race, ethnicity, gender, disability, sexual orientation, gender identity, national origin, tribe, caste, socio-economic status, thinking and communication styles, etc.), collectively and as individuals. ACS seeks to proactively engage, understand, and draw on a variety of perspectives.

Inclusion**
Builds a culture of belonging by actively inviting the contribution and participation of all people. Every person's voice adds value, and ACS strives to create balance in the face of power differences. In addition, no one person can or should be called upon to represent an entire community.

Respect
Ensures that each person is treated with professionalism, integrity, and ethics underpinning all interpersonal interactions.

https://www.acs.org/diversity

14

14

ACS Advocacy

See your influence in action!

The impact and results of **ACS member advocacy** outreach and efforts by the numbers!

2439+ Members participated In Act4Chemistry	1739+ ACS Advocacy Workshops participants or enrollees	49 Years of Public Policy Fellows	2000 Letters sent to Congress
Get Involved	Enroll in a workshop	Become a Fellow	Take Action

American Chemical Society

https://www.acs.org/policy

15

15

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ACS ON CAMPUS

16

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- **ACS Industry Matters**

ACS member only content with exclusive insights from industry leaders to help you succeed in your career. #ACSIndustryMatters

Preview Content: acs.org/indnl

- **ACS Innovation Hub LinkedIn Group**

Connect, collaborate and stay informed about the trends leading chemical innovation.

Join: bit.ly/ACSinnovationhub

17

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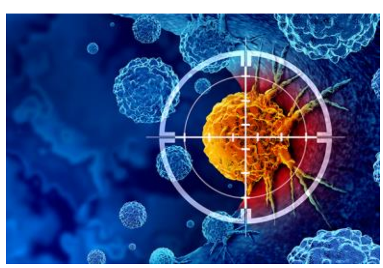
Wednesday, October 18, 2023 | 12-1:30pm ET

A Bond Worth Forming: The Rise of Targeted Covalent Inhibitors

Co-produced with *NCW*, ACS Publications, and ACS Division of Medicinal Chemistry



Thursday, October 19, 2023 | 2-3:30pm ET

A Bond Worth Forming: The Rise of Targeted Covalent Inhibitors

Co-produced with *NCW* and CAS, a division of the American Chemical Society

Miercoles, 1 de Noviembre, 2023 | 2-3pm ET

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19

19


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20

20

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ACS Green Chemistry Institute
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Established in 2005, the ACS GCIPR is an organization dedicated to catalyzing the integration of green chemistry and engineering in the Pharmaceutical industry

abbvie, AMGEN, AstraZeneca, BAYER, Biogen, biohaven pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, GILEAD, gsk, IPSEN, Janssen, Lilly, MERCK, NEUROCRINE BIOSCIENCES, NOVARTIS, novo nordisk, Pfizer, Roche, Takeda, ucb, VERTEX, Merck KGaA Darmstadt, Germany, ASYMCHEM, BACHEM, CatSci, CODEXIS, HIKAL, Hovione, INNOSYN, Kaneka, novasep, PHARMARON, PolyPeptide GROUP, PORTON, Sai, SK pharmteco, SOLARA, WuXi AppTec, CORTEVA agriscience, PHT, ACS Green Chemistry Institute

Mission and Strategic Pillars

ACS Green Chemistry Institute
Pharmaceutical Roundtable

Tools and Metrics for Innovation

Influencing the Research Agenda

Educating Leaders

Global Collaboration

Peter J. Dunn Award

for Green Chemistry & Engineering Impact
in the Pharmaceutical Industry

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Excellence in R&D and execution of pharmaceutical green chemistry

Compelling environmental, safety and efficiency improvements over existing technologies

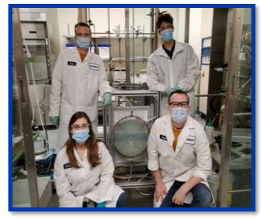
Established in 2016

2020

Dan Bailey

Takeda

2021



- Stephen Dalby
- Francois Levesque
- Cecilia Bottecchia
- Jonathan McMullen

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2022

- Karla Camacho Soto
- Mike DiMaso   Di-Mah-So
- Jacob Forstater – Fore-Staaah-ter
- Nadine Kuhl - Nadine COOL
- Reed Larson
- Chris Prier
- Ben Turnbull

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2024 Nominations open Fall 2023: https://www.acsgcipr.org/awards/

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for Green Chemistry & Engineering Impact
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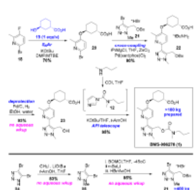

Scheme 2: 2nd Generation Endoame & Triazole Synthesis

- Micheal Smith
- Yichen Tan
- Candice Joe
- David George
- Michael Dummeldinger
- Harshkumar Patel
- Richard Fox
- Shane McKenna
- Zara Seibel
- Stephan Jenne

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Two is better than one!

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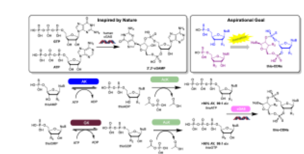
- Atom Economy
- Catalysis
- Reduction of Solvents and Auxiliaries
- Waste Prevention



Scheme 2. Assembly of Triphosphates and CDNs via Biocatalytic Pathways.

- John McIntosh
- Chihui An
- Jeffrey C. Moore
- Matthew S. Winston
- Jennifer V. Obligacion
- Nastaran Salehi Marzijarani
- Zhijian Liu
- Feng Peng
- David J. Lamberto
- Xiaodong Bu

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Sustainable Manufacturing of BMS-986278 Leveraging an ERED/KRED Biocatalytic Cascade

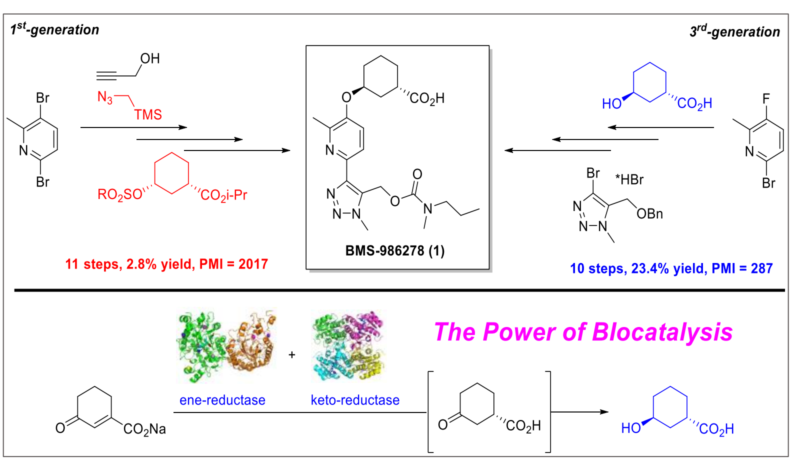
ACS Webinar
Oct 12th, 2023

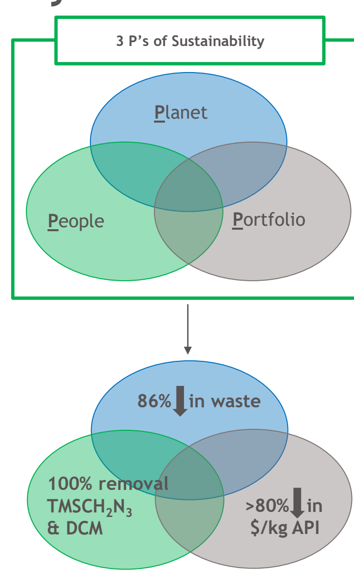
Bristol Myers Squibb™

Dr. Harshkumar Patel
Harshkumar.patel@bms.com

Bristol-Myers Squibb
Chemical & Process Development (CPD)

2023 Peter J. Dunn Award: Overall Summary





2023 Peter J. Dunn Award: Overall Summary

Bristol Myers Squibb


Mike Dummeldinger


Rich Fox


David George


Candice Joe

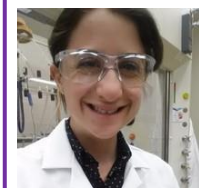

Shane McKenna


Harshkumar Patel


Mike Smith


Yichen Tan

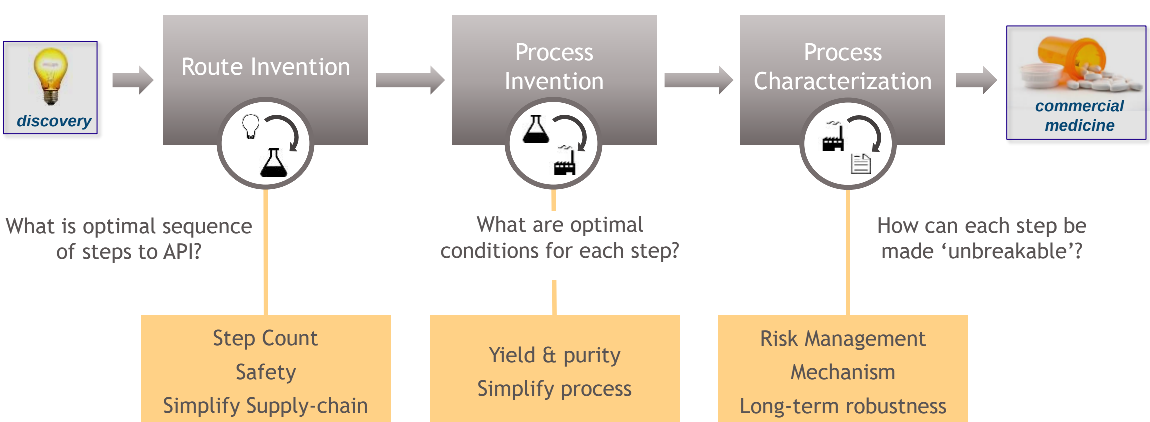
CODEXIS


Zara Seibel


Stephan Jenne

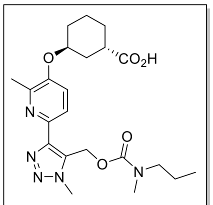
Our Approach

CPD Mission: Create <u>safe</u>, <u>economic</u>, and <u>sustainable</u> processes to supply high quality active ingredients for the medicines we deliver to patients

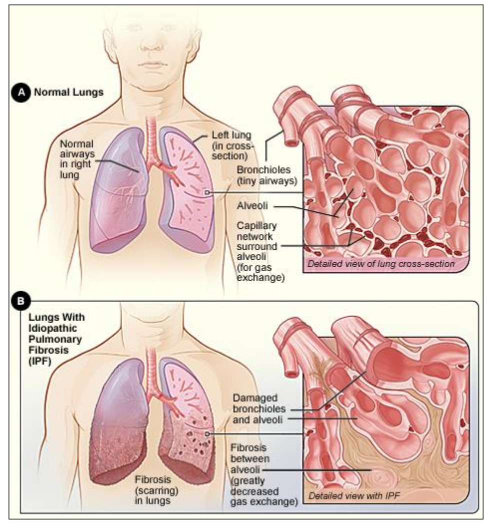


Program Background

- BMS-986278 is currently under development for treatment of Idiopathic Pulmonary Fibrosis (IPF) + other ILD (Interstitial Lung Diseases)
  - IPF affects ~200K in US and ~50K new cases per year (worldwide)
  - Increasing incidence, prevalence and severity
  - Most prevalent of the fibrosing lung diseases - doubling in the last decade
  - Avg life expectancy after diagnosis = 3-5 years



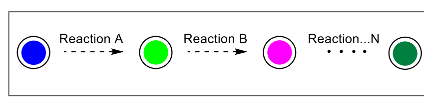
BMS-986278

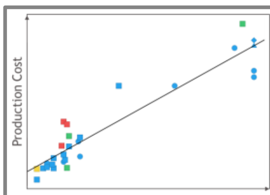


29

Towards a Proposed New Route: *Using Modelling & Prediction*

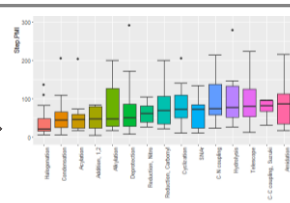
$$\text{Process mass intensity (PMI)} = \frac{\text{quantity of raw materials input (kg)}}{\text{quantity of bulk API out (kg)}}$$





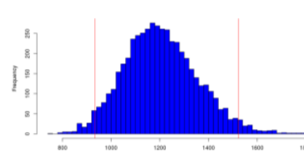
PMI correlates to production cost

understand



Step PMI is unique and can be predicted

simulation



Overall route PMI can be simulated

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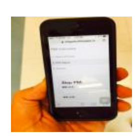
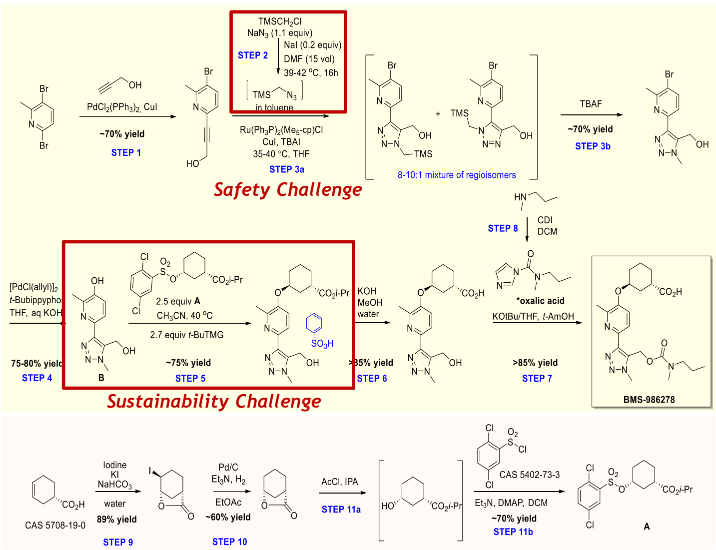
Shiny Web App PMI Predictor



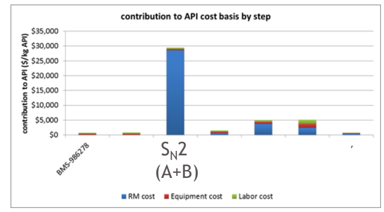
https://acsgcipr-predictpmi.shinyapps.io/pmi_calculator/

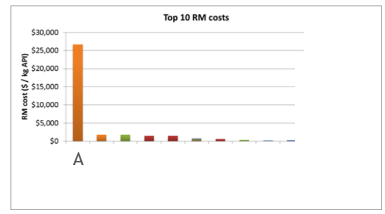
30

Background: Enabling Route for 8-30 kg Deliveries



Overall: 11 total steps; Longest Linear Sequence: 7 steps



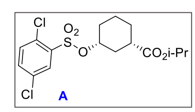


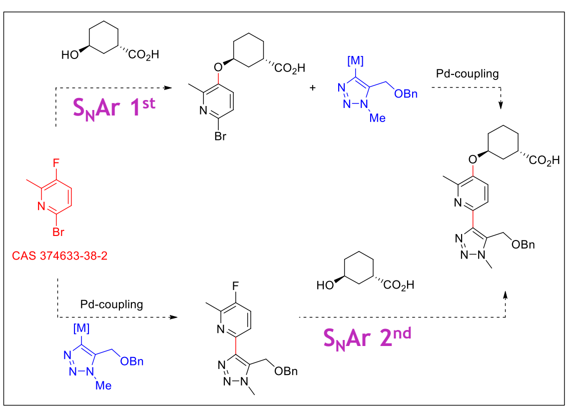
Safety: challenges associated with preparation and use of hazardous Azide, $TMSCH_2N_3$ and Cu

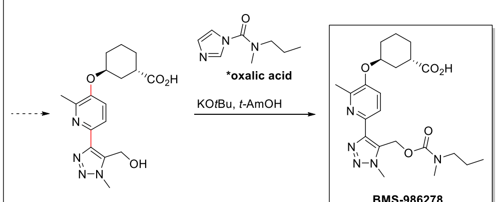
Sustainability: Complex fragment used in excess, results in significant cost/waste

31

Strategy for New-Route Development







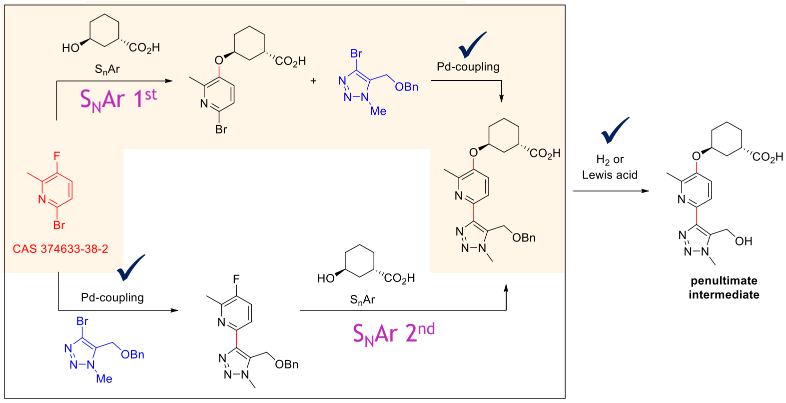
Predictions:

- >50% reduction in overall *cost* and PMI to API

- Opportunity to use cyclohexyl side chain fragment as limiting reagent (vs 2.5 equiv A)
- Eliminates azide safety risks
- Maintains same API step
- Two reaction sequences possible (optionality)
- Requires POC for proposed end-game AND syntheses of new triazole and *trans*-hydroxy acid fragments

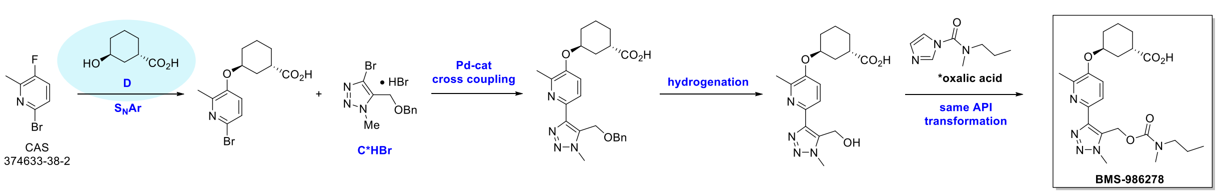
32

Fragment Coupling Decisions

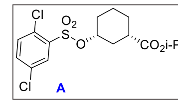


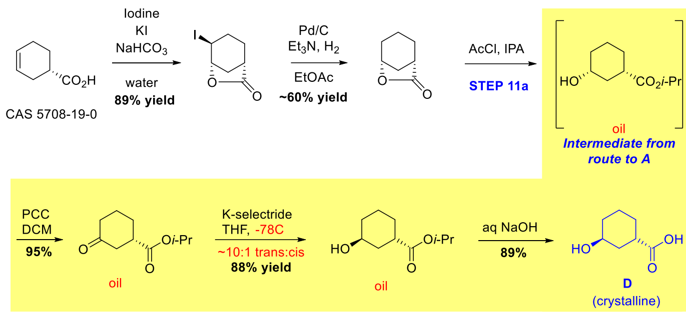
- No red flags wrt OBn deprotection conditions to afford penultimate intermediate
- No significant differences between either Pd coupling under initial Kumada conditions
- **S_NAr 1st approach selected since more reactive S_NAr system/decreased impurities**

Overall Planned Endgame



Preparing Fragment ‘D’ for POC of Endgame

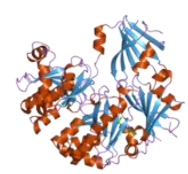


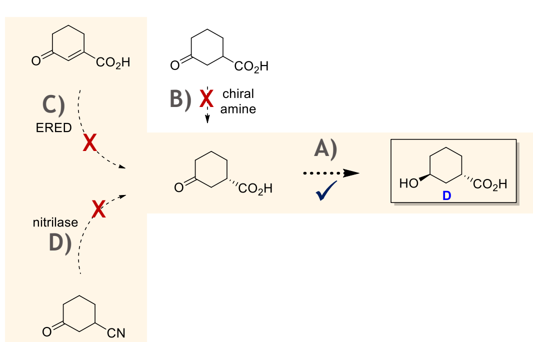


This enabled the preparation of initial lab supplies of ‘D’, but was not planned for bulk quantities

Initial Route Scouting to ‘D’:

Biocatalysis (i.e., use of enzymes) was initial focus….





A) Achieved POC using KRED P2-G03

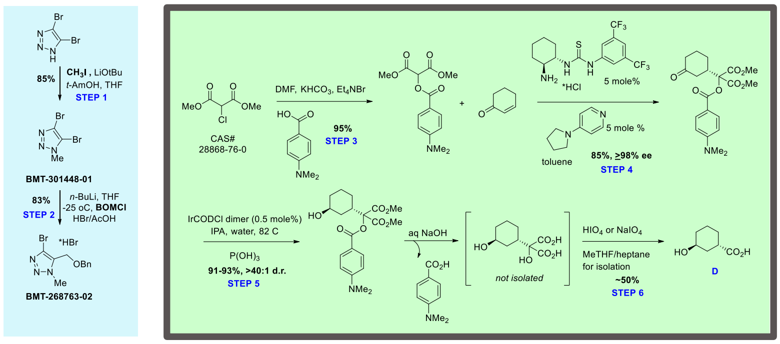
B) No resolution hits

C) No good hits with commercial enzyme kits

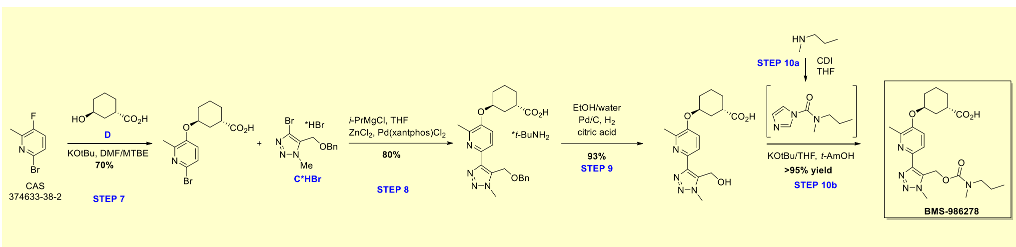
D) No good hits with commercial enzyme kits

…but did not lead to quick POC

2nd-Gen Route to Prepare >100 kg BMS-986278

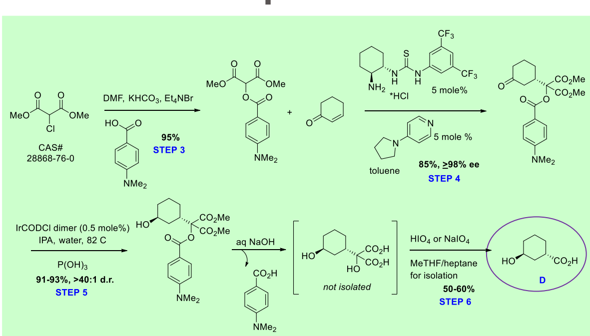


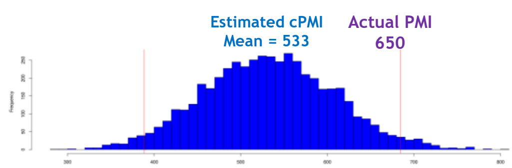
- 1st time scale-up produced 120 kg API
- Route to 'D' not expected to be 'long-term'



37

Initial Development & Scale-Up to BMS-986278

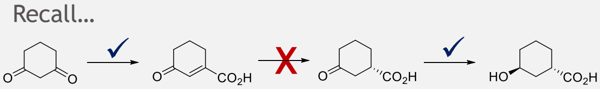




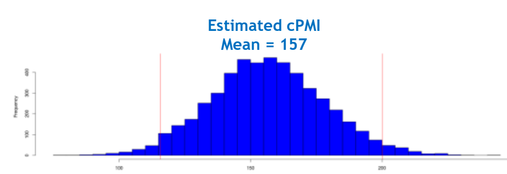
Tools Predicted Enzymatic Route to 'D'→
- >50% reduction in PMI
- 20-50% cost reduction

With POC for end-game, can we return to envisioned ERED/KRED cascade, *w/ a focus on enzyme evolution?*

Recall...

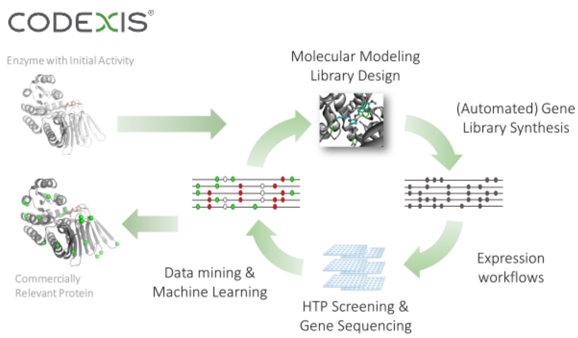


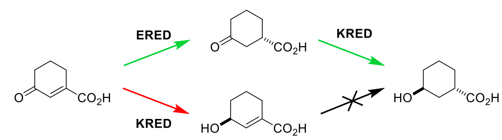
No hits with commercial ERED's   *POC using KRED P2-G03*



38

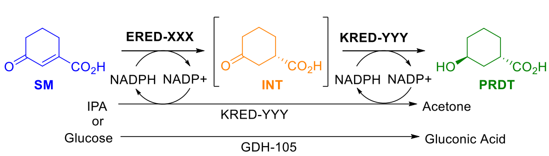
CodeEvolver® Directed Evolution Platform for API Manufacturing

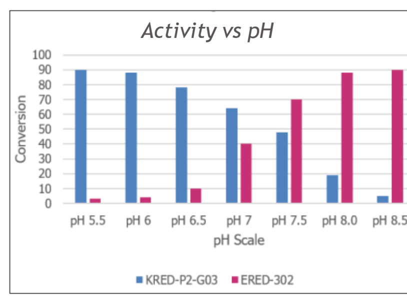


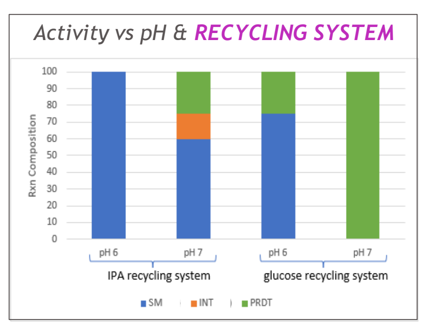


Key performance indicators: *target*
Substrate loading → >50 g/L
ERED * KRED loading → <12 wt% total
Conversion & selectivity → >98% @ >99% de/ee

Screening & Early Evolution

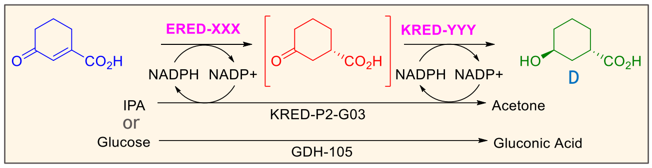






- After 2 rds of evolution (IPA recycling system @ pH 6):
  - Obtained POC, but: 100 wt% ERED, 100 wt% KRED and only 5 g/L SM loading
- Before continuing with evolution, conducted some initial process development. Data supported:
  - pH 7 (vs pH 6) optimal for ERED/KRED cascade
  - Glucose/GDH significantly outperformed IPA recycling system
- Led to major shift in enzyme evolution conditions….

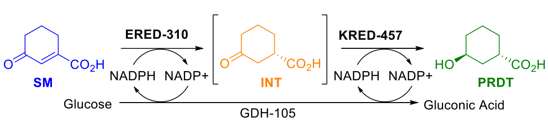
Results from a Key Partnership in Enzyme Evolution



	POC Conditions	Conditions after 11 Rounds of Evolution + Process Development
Enzyme	ERED-001 KRED-P2-G03	ERED-310 KRED-457
Substrate Load	5 g/L	67 g/L
ERED Load	100 wt%	8 wt%
KRED Load	100 wt%	3 wt%
Recycling System	IPA (20%)	Glucose + GDH
pH	6	7
Temperature	30C	30C
Time	21 hours	12 hours
Pdt/Int/SM	75/15/10	99/0/0
Selectivity	>99% ee, >99% de	>99% ee, >99% de

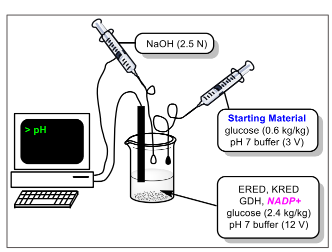
Key performance indicators:	*target*
Substrate loading	→ >50 g/L ✓
ERED * KRED loading	→ <12 wt% total ✓
Conversion & selectivity	→ >98% @ >99% de/ee ✓

Going from Lab to Plant Scale



<u>1st Gen Process:</u>

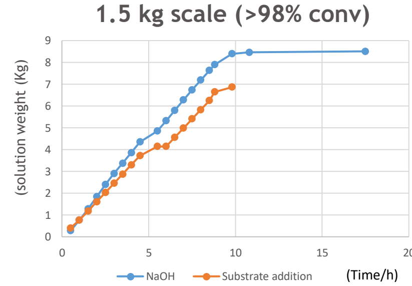
- SM added as soln over ~10 h to soln of ERED/KRED/GDH & NADP+
- As rxn proceeds, gluconic acid forms and pH drops
- pH is continuously monitored and aq NaOH dosed to maintain pH ~7
  - ➢ Overall, aq NaOH addition curve serves as PAT for conversion



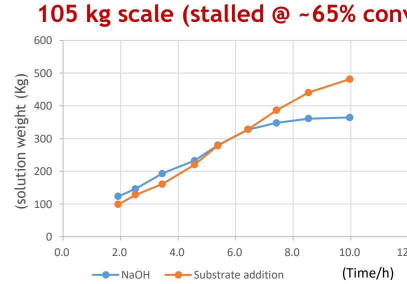
<u>Results:</u>

- No issues on 1.5 kg scale
- Stalling observed on 105 kg scale

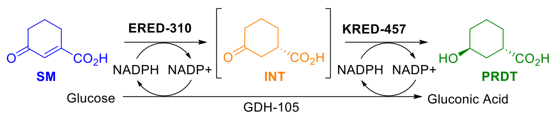
1.5 kg scale (>98% conv)



105 kg scale (stalled @ ~65% conv)



Troubleshooting the ERED/KRED Cascade

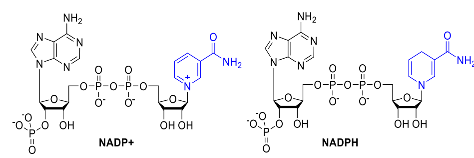


Results:

- Took slipstreams of stalled 105 kg rxn mixture and added either:
  - KRED only ⟶ no significant change
  - ERED only ⟶ no significant change
  - GDH-105 only ⟶ no significant change
  - NADP+ only ⟶ complete conversion
- NADP+ charge alone recovered activity
- Since oxidation of glucose by GDH-105 is very fast → proposed NADPH is predominant species during reaction
- Additional expts supported while NADPH is stable at pH 10-13, it has some stability issues at pH 7 (note: NADP+ is stable for >24 h at pH 7)
- *How can we leverage this info to develop a more robust process……*

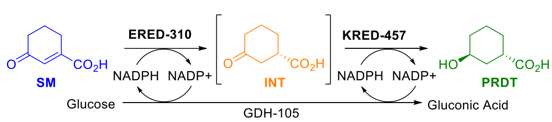
Who was the bad actor?

***Poll Question**: Answer on Interactive Screen*



43

New Protocol & Scale-Up Results

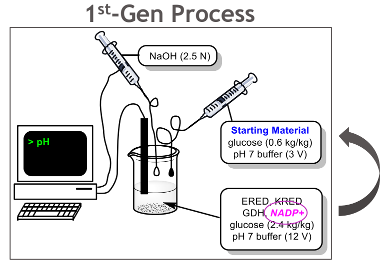


- ….add NADP+ in SM solution (vs enzymes) to minimize build up of NADPH

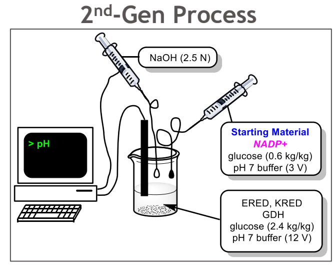
200 kg batch w/ revised solution prep:
- >98% conv; no kickers needed
- 87% isolated yield
- 100% chiral purity

✓

1^{st}-Gen Process



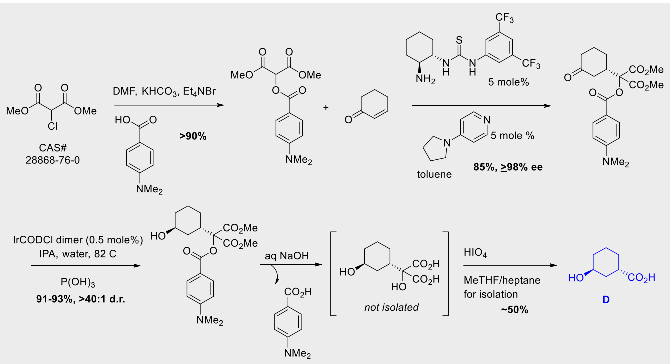
2^{nd}-Gen Process



44

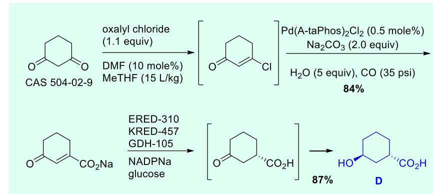
Comparison of Routes to 'D'

Enabling Route to 'D'



Compound D from Enabling Route | Compound D from ERED/KRED route

New Route to 'D'

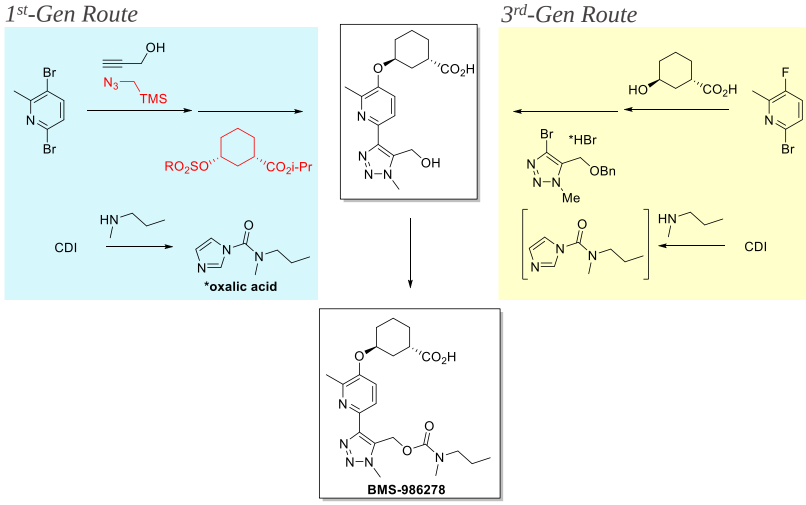


	Enabling Route	ERED/KRED Route
Step Count	4	2
Overall Yield	35%	73%
Est Cost Saving	-	>50% savings in $/kg final API
PMI	650	112

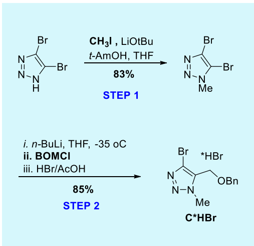
PMI: kg of all inputs leading to 1 kg of Compound D

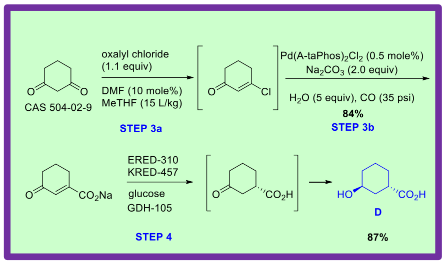
Overall Route Modifications

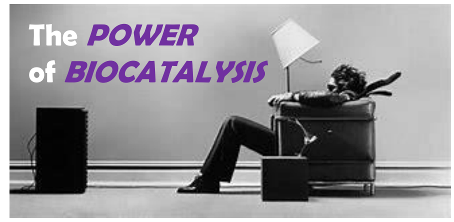
1st-Gen Route | *3rd-Gen Route*

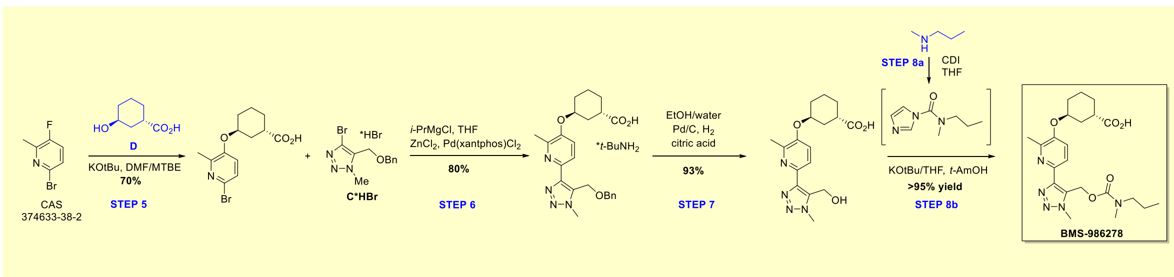


Optimized Route to BMS-986278









Overall Route Metrics Summary

2023 Co-WINNER | ACS GCIPR Peter J. Dunn Award for Green Chemistry & Engineering

Social/People

- 100% elimination of *hazardous* $TMSCH_2N_3$ & dichloromethane (DCM)

eliminates 339 kg $TMSCH_2N_3$ & >39,000 kg DCM per *100 kg* API delivered!

Environmental/Planet

- >8x yield ⬆ vs Ph2 route
- 50% ⬇ in steps needing aq wkup
- ⬇ 86% reduction in overall PMI

eliminates 6 million Kg of waste annually at peak!

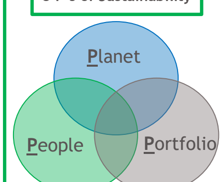
Economic/Portfolio

- ⬇ 60% reduction in $/kg API (100 kg scale)

>$3M in cost avoidance to deliver 1st *100 kg* API

- ⬇ expect >80% reduction in $/kg API on >1000 kg scale….

3 P's of Sustainability



"the triple bottom-line"

Embedding 'Green By Design' principles as part of our development mindset to deliver ***enhanced value to our People & Patients***

Acknowledgements

LPA1#2 Project Team (CT/Ph2)

- Rich Fox (PL/CL)
- Carlos Guerrero
- Steve Wisniewski
- James Chadwick (AL)
- Jeff Nye (EL)
- Eric Saurer (EL)
- Sivaraj Ramasamy + BBRC team
- Sabuj Mukherjee

Automation/Catalysis Groups

- Grace Chiou
- Jake Janey
- Candice Joe
- Jun Qiu, Hui Li, Qiao Zhou
- Vic Rosso
- Eric Saurer
- Eric Simmons
- Jay Stevens
- Shulin Wu

LPA1#2 Project Team (New Route)

- Simi Bright
- Amaris Borges Muñoz
- James Chadwick
- Mike Dummeldinger
- Rich Fox (PL)
- David George
- Carlos Guerrero
- Nate Kopp
- Ziqing Lin
- Mark Lindrud (SL)
- Shane McKenna
- Jeff Nye (TL)
- Harshkumar Patel
- Dan Perkins
- Damian Reyes Luyanda
- Eric Saurer
- Dimitri Skliar (EL)
- Mike Smith (CL)
- Yichen Tan
- Peter Tattersall (AL)
- Alice Yang
- Shasha Zhang

OccTox/GIAC/EIAC

- Lydia Breckenridge
- Jessica Graham
- Penny Leavitt
- Max Soumeillant
- Rodney Parsons
- Sharla Wood

IDT

- Jimmy Bhatt
- Peter Cheng
- Vidya Iyer
- Scott Jones
- Susanne Kiau
- Laxma Kolla
- Irena Maksimovic
- Miguel Rosingana
- Emily Reiff
- Clyde Sharik
- Lakshmi Sivaraman
- Robin Stevens
- Sue Sultzbaugh

CPD + BBRC Senior Leadership Teams

ACS Green Chemistry Institute
Chemistry for Life®

DPST, ASO

- Colin Chan
- Mohan Kanthasamy
- Chris Levins
- Adriene Malsbury
- Kyle Martin
- Anisha Patel

API Ops

- Mike Cassidy
- Sabrina Ivy
- Simon Leung
- Mark Lindrud
- Christina Risatti
- Jin Zhang
- Shasha Zhang

Codexis

- David Entwistle
- Stephan Jenne
- Zara Seibel

Bristol Myers Squibb | Chemical & Process Development 49

49

Bristol Myers Squibb™

50

Green Manufacturing of STING Agonist MK-1454 Leveraging a Kinase-cGAS Enzymatic Cascade

ACS Green Chemistry Institute

Peter Dunn Award Webinar

12 October 2023

MERCK
INVENTING FOR LIFE

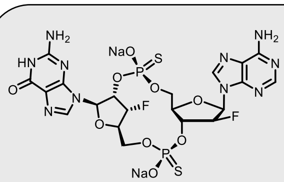
Matthew S. Winston, Ph.D.
Principal Scientist, Biocatalysis

Merck & Co., Process Research and Development, Rahway, NJ

P Public

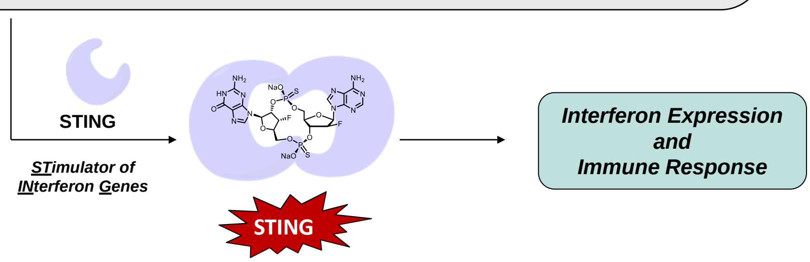
51

MK-1454: A Challenging Synthetic Target



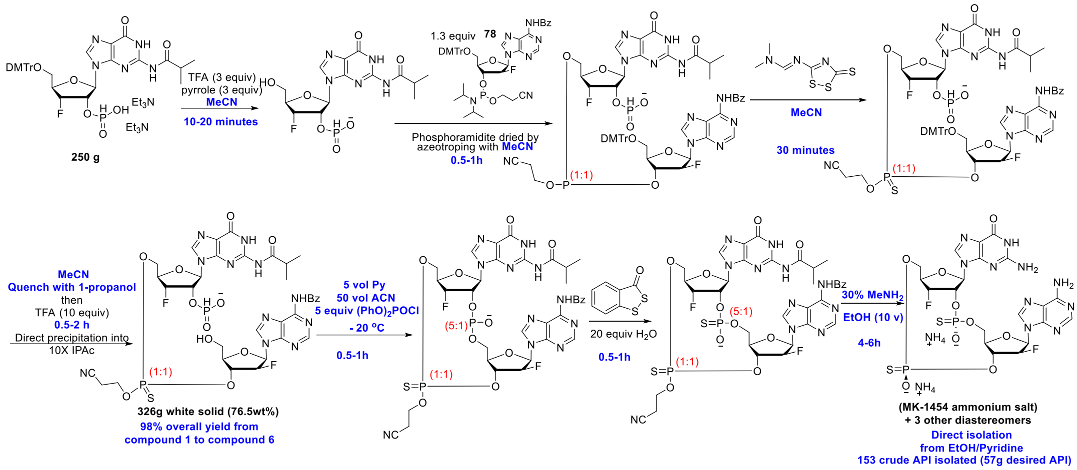
MK-1454
Immuno-oncology

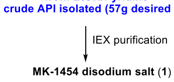
Key Synthetic Challenges
- 10 stereocenters, including 2 at phosphorus
- 2 unnatural nucleosides with fluorinated stereocenters
- 13-membered macrocyclic core
- Unsymmetrical 2'5' and 3'5' linkages



52

1st Generation Route





8 steps from advanced intermediates
30% overall yield
Chromatography required
PMI ~ 9,000

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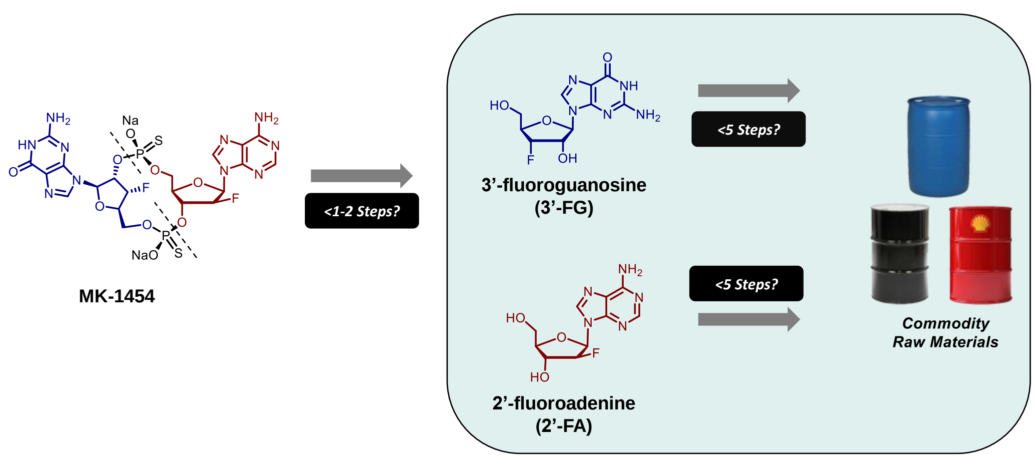
53

From Commodity to Active Pharmaceutical Ingredient (API)



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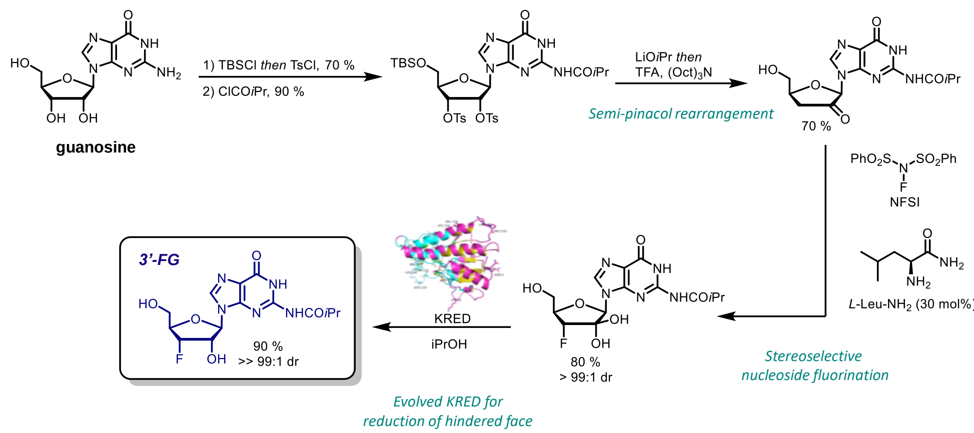
54

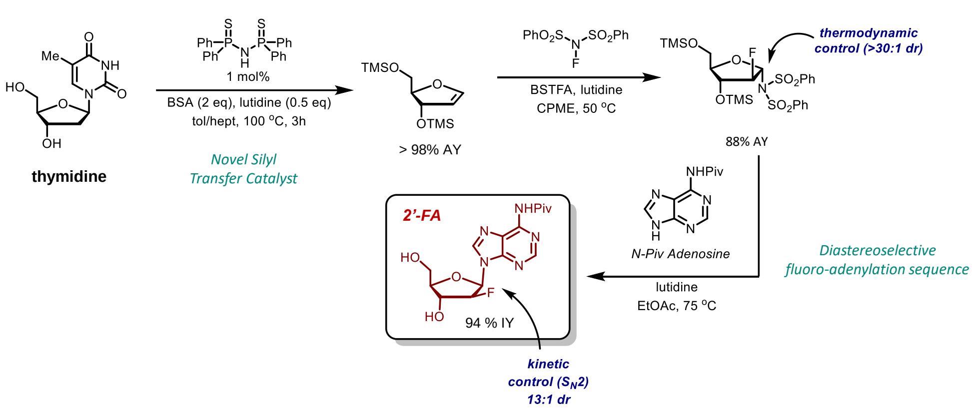
Overview of 3'-F-Guanosine (3'-FG) Process



Benkovics, T. *et al. J. Am. Chem. Soc.* **2022**, *144*, 5855.

55

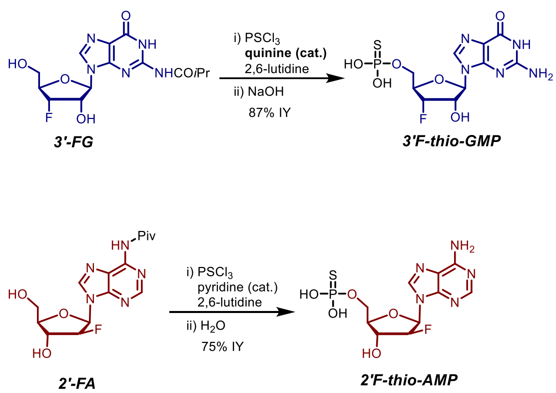
Overview of 2'-F-Adenosine (2'-FA) Process

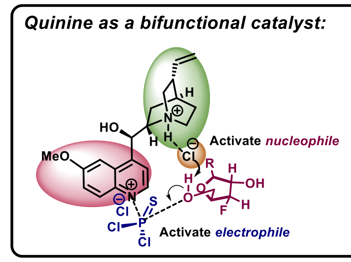


Benkovics, T. *et al. J. Am. Chem. Soc.* **2022**, *144*, 5855.

56

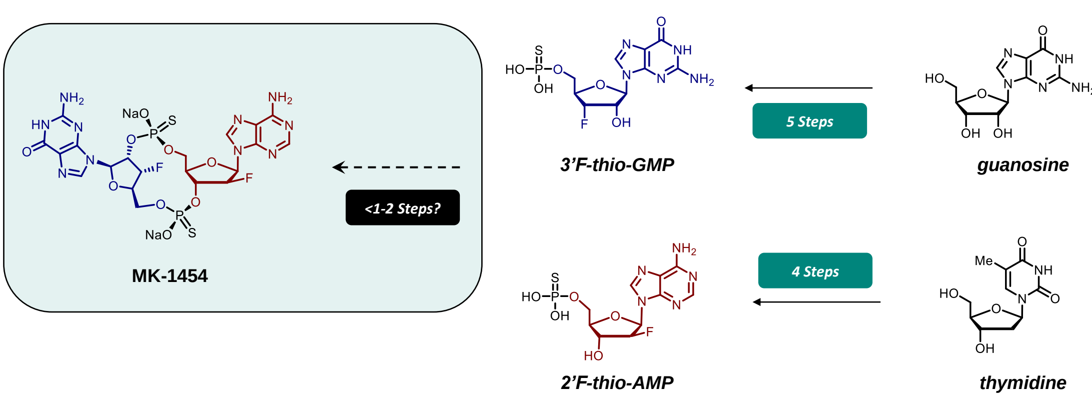
Organocatalytic Thiophosphorylation





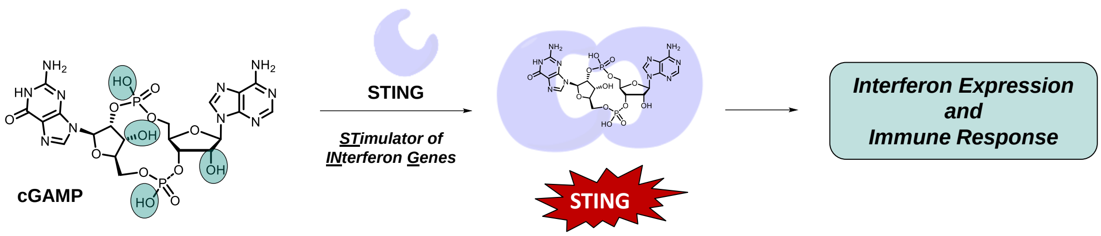
Marzijarani *et al* *J. Am. Chem. Soc.* **2020**, *47*, 20021.

From Commodity to API



What is the most direct route from monomers to MK-1454?

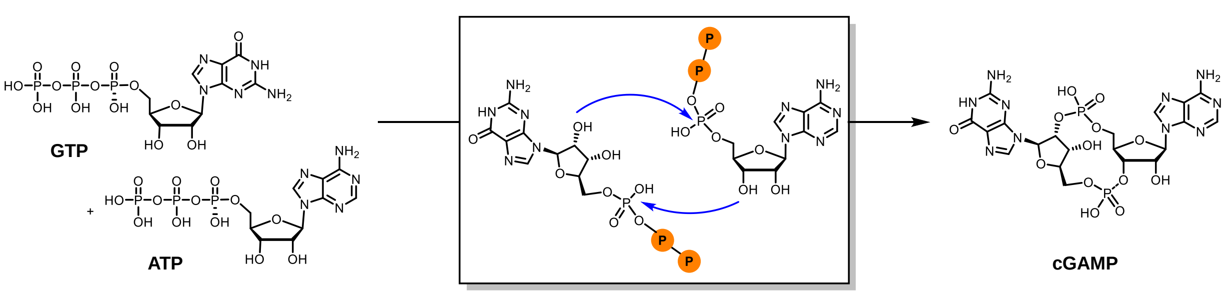
Taking Cues from Biology: cGAMP Mechanism of Action



MK-1454 is an analog of natural signaling molecule cGAMP

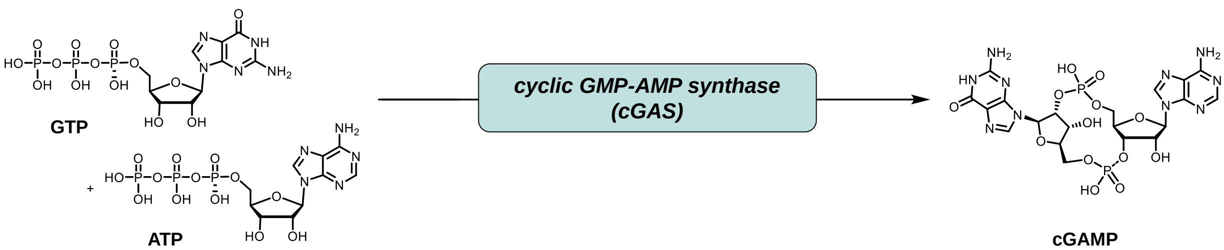
Sun, L. *et al. Science* **2013**, 786

Taking Cues from Biology: cGAMP Biosynthesis



Sun, L. *et al. Science* **2013**, 786

Taking Cues from Biology: cGAMP Biosynthesis



Sun, L. *et al. Science* **2013**, 786

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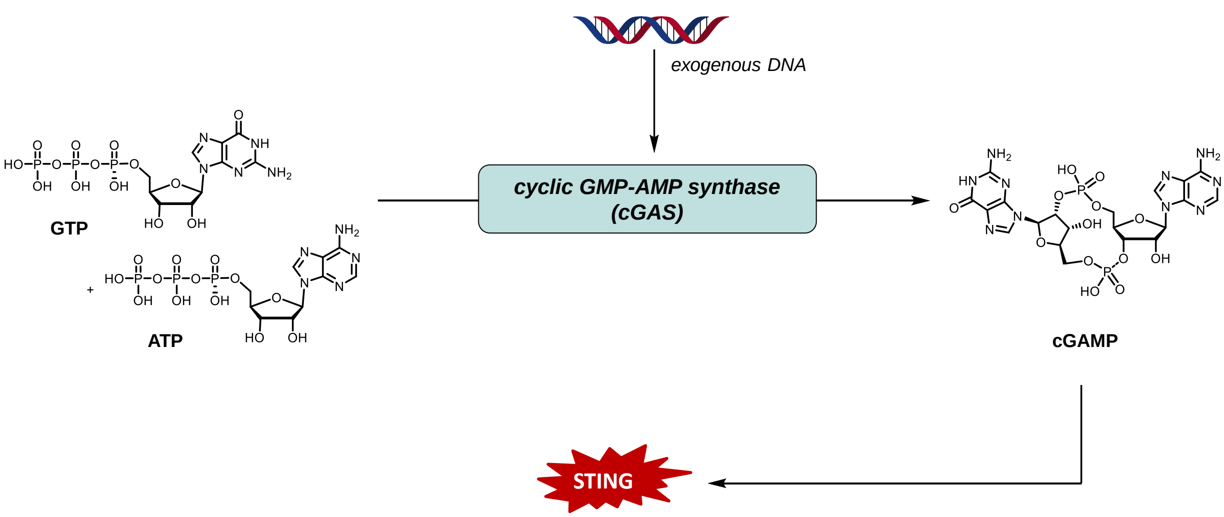
61

Taking Cues from Biology: cGAMP Biosynthesis



Sun, L. *et al. Science* **2013**, 786

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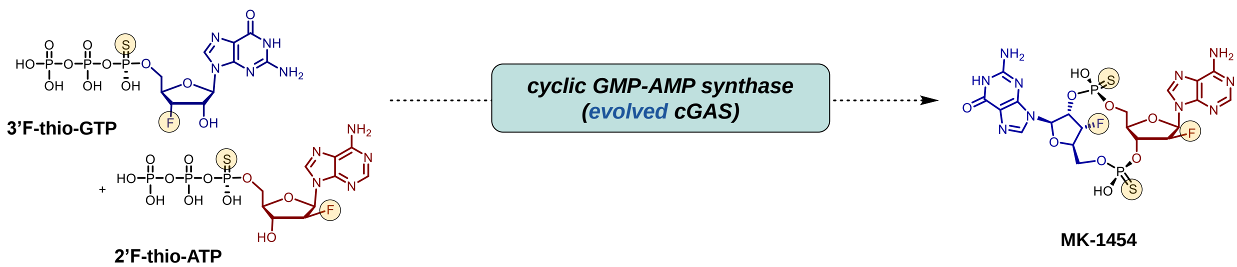
62

Drawing Inspiration from Nature to Make MK-1454



Can we engineer cGAS to produce MK-1454?

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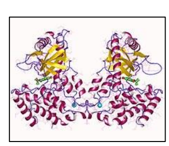
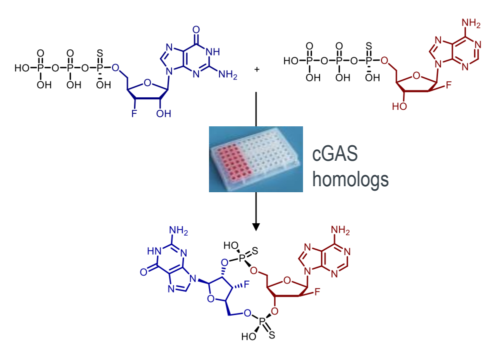
63

Discovery of a Promiscuous Wild-Type cGAS

Express and screen animal cGAS homologs for trace activity

Bioinformatics → Express in *E. coli* → Lyse cells → Screen for reactivity on authentic substrates





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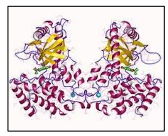
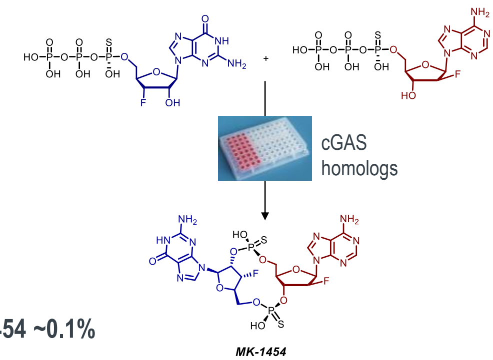
64

Discovery of a Promiscuous Wild-Type cGAS

Express and screen animal cGAS homologs for trace activity

Bioinformatics → Express in *E. coli* → Lyse cells → Screen for reactivity on authentic substrates





Screening hit!
cGAS from bald eagle: **MK-1454 ~0.1%**
+ 2 other diastereomers

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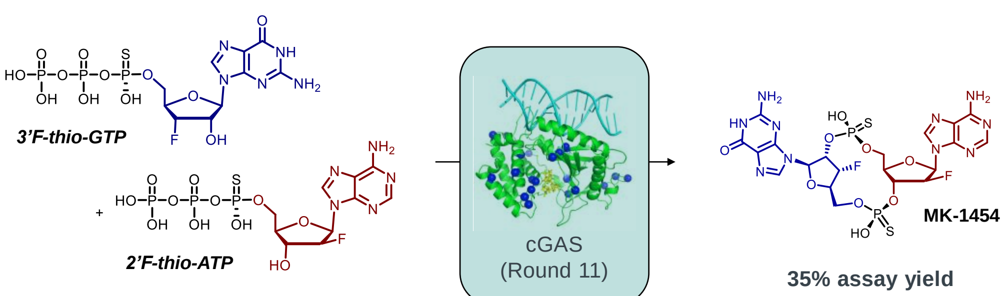
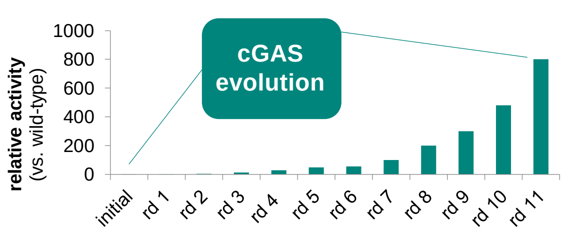
65

Directed Evolution of an MK-1454-Producing cGAS



35% assay yield
single diastereomer



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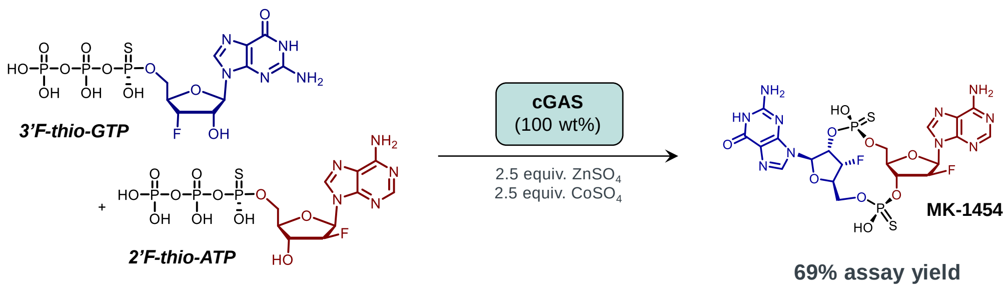
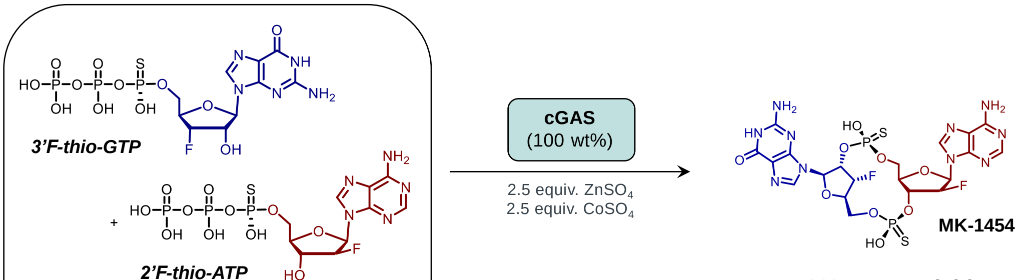
66

Directed Evolution of an MK-1454-Producing cGAS



69% assay yield
>99% de

Directed Evolution of an MK-1454-Producing cGAS

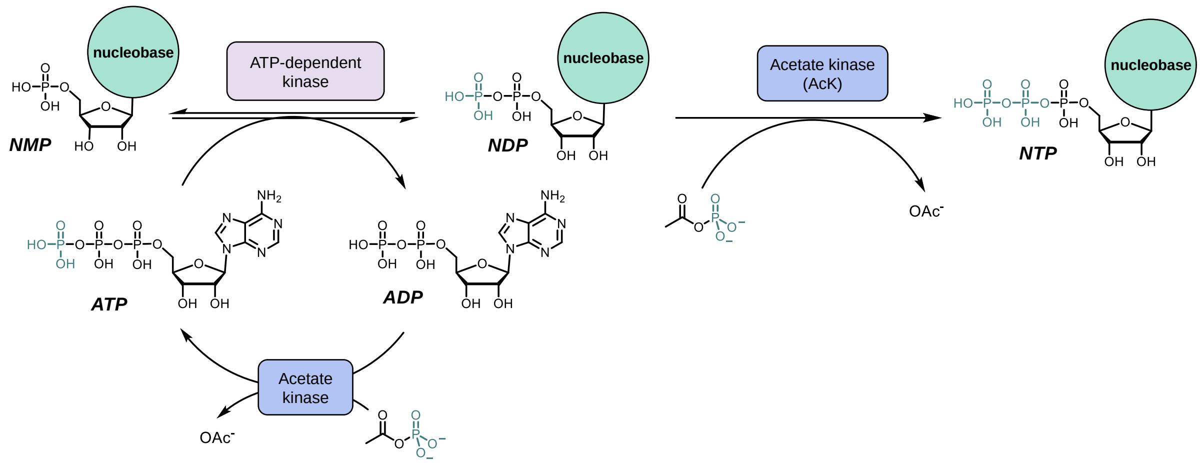


Challenge: Isolation, handling and stability of thiotriphosphates

69% assay yield
>99% de

Can we produce nucleotide triphosphates in situ?
(Biocatalytic cascade!)

Taking Cues from Biology: Nucleotide Triphosphate Synthesis



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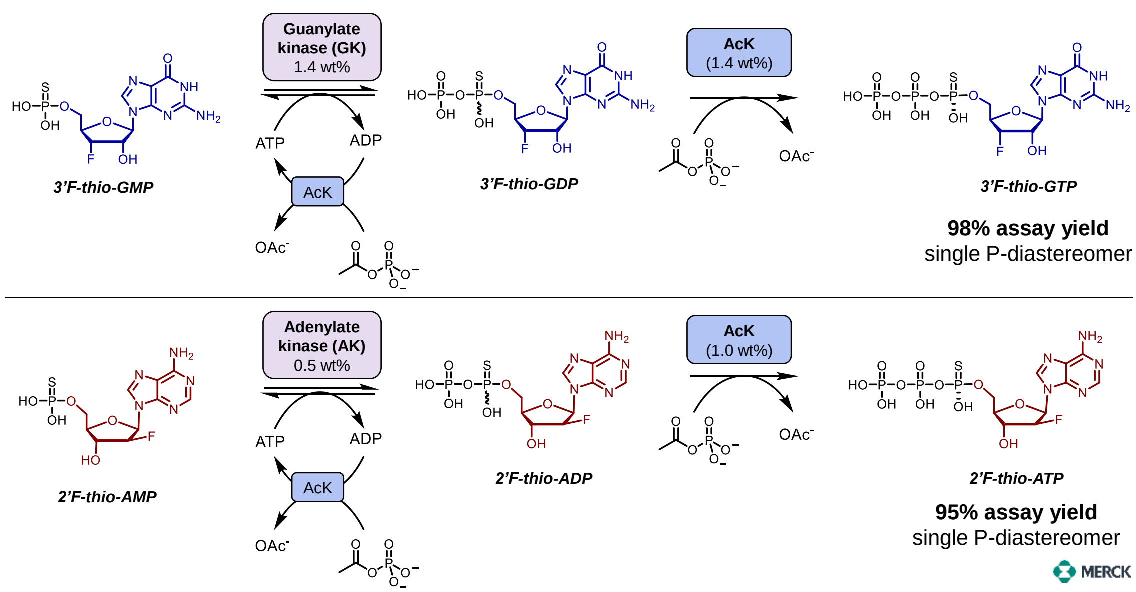
Protein Engineering Enables Phosphorylation of Unnatural Nucleotides



98% assay yield
single P-diastereomer

95% assay yield
single P-diastereomer

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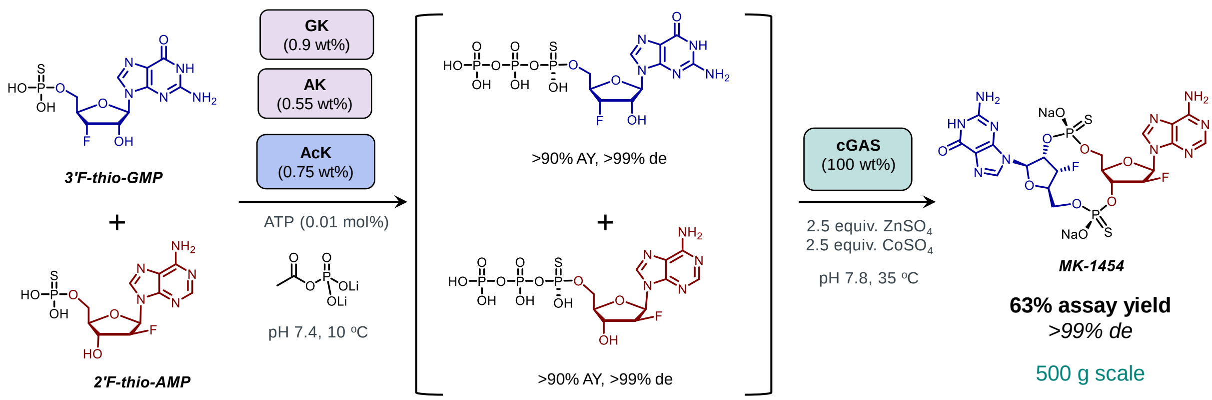
Clicking Together Nucleotides in Telescoped Enzymatic Cascade



Single-pot enzymatic cascade!

McIntosh, J. A. *et al.* *Nature* **2022**, *603*, 439.

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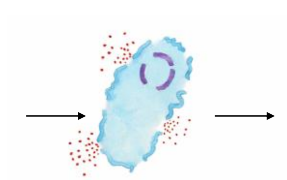
71

Lyophilized Cell Lysates As Standard Biocatalyst Sources

Biocatalyst overexpression in E. coli fermentation



cell lysis

Lyophilization

Added directly to reactions without purification

Biocatalyst

Bacterial host cell protein

Bacterial genetic material

Bacterial endotoxins

Lipids

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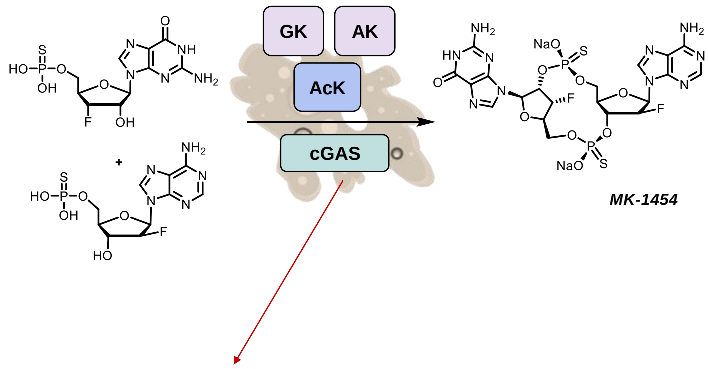
72

Post-synthetic Process Chemistry Challenges

MK-1454 is injected into patients

Higher standard for API purity compared to orally administered drugs



E. coli lysed cell powder can elicit adverse immune response

Challenge! Protein in final product must be undetectable (<20 ppm)

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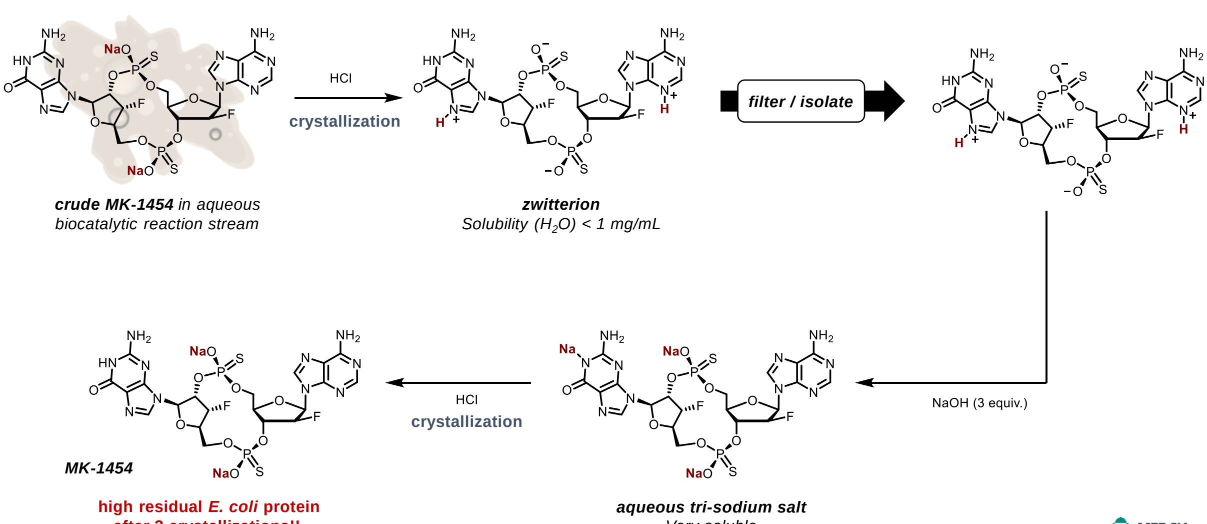
73

Sequential Crystallizations of MK-1454



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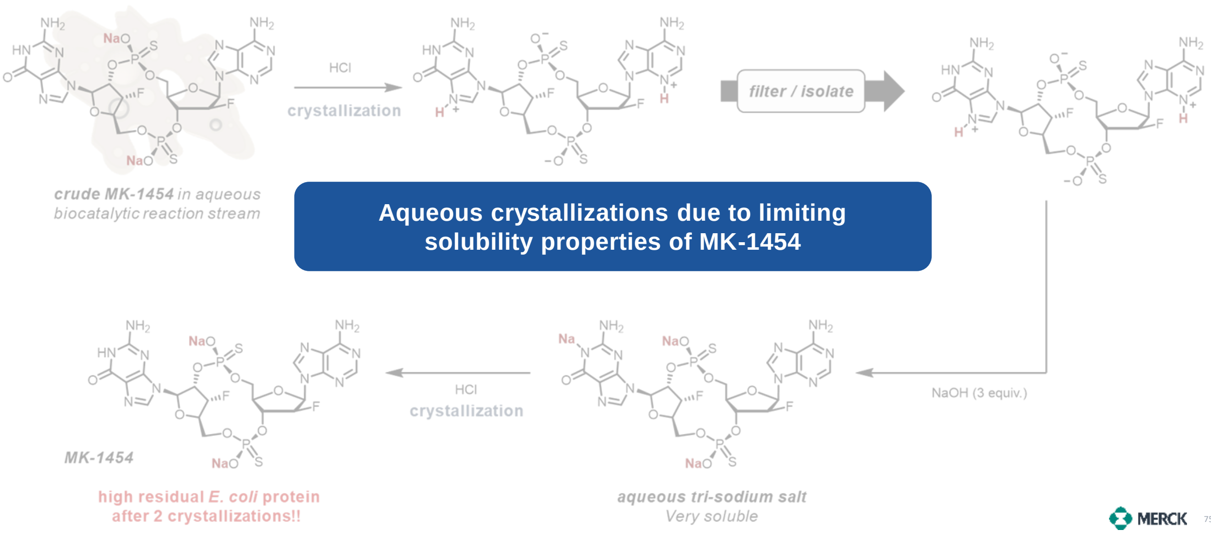
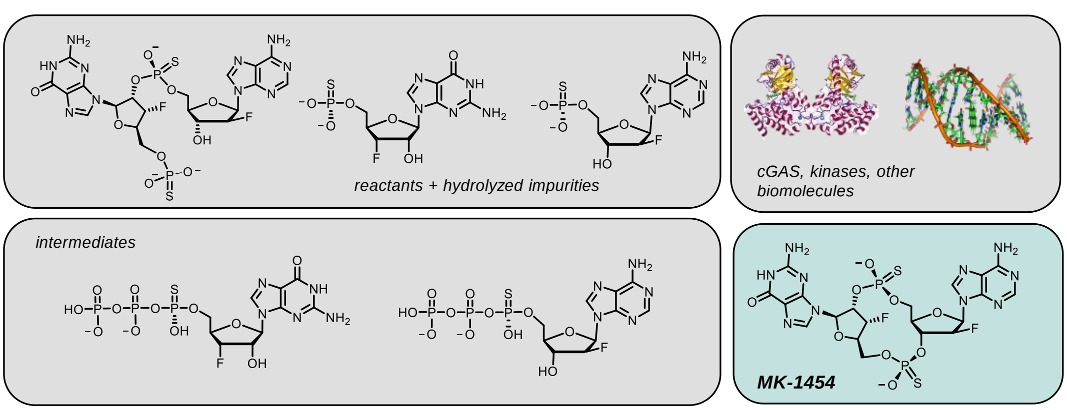
74

Sequential Crystallizations of MK-1454



75

Workup and Isolation Challenges



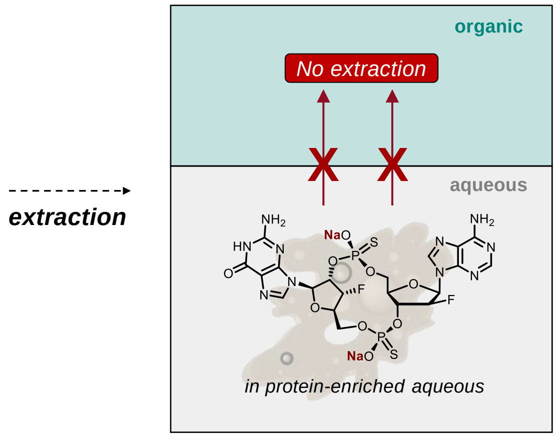
Like MK-1454, **major impurities** are highly polar, highly soluble in water, and poorly soluble in organics

76

Poor Extraction of MK-1454 Into Organic Solvents

MK-1454 is insoluble in most organic solvents

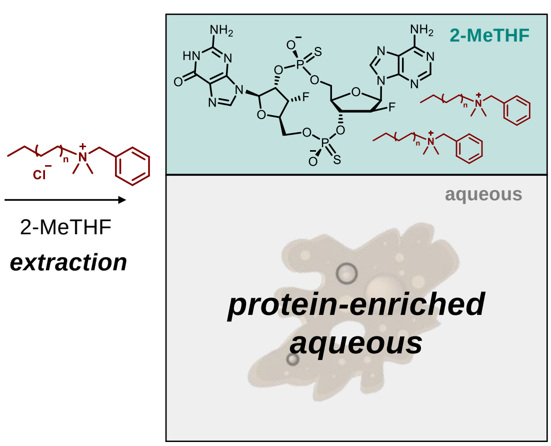
end-of-reaction slurry

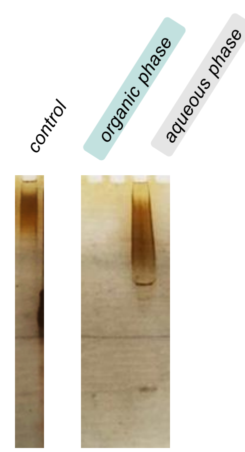


77

Quaternary Ammonium Extractants for MK-1454 Purification

end-of-reaction slurry

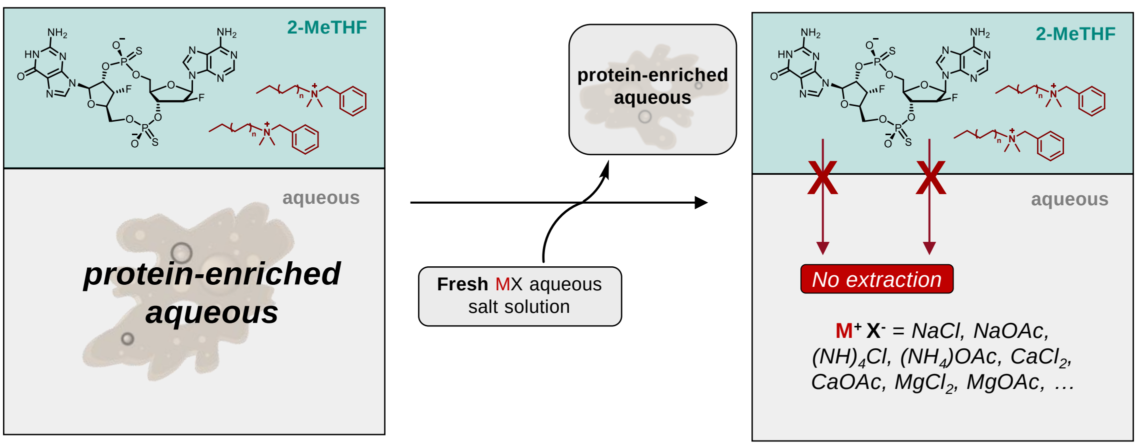




No detectable protein in organic layer

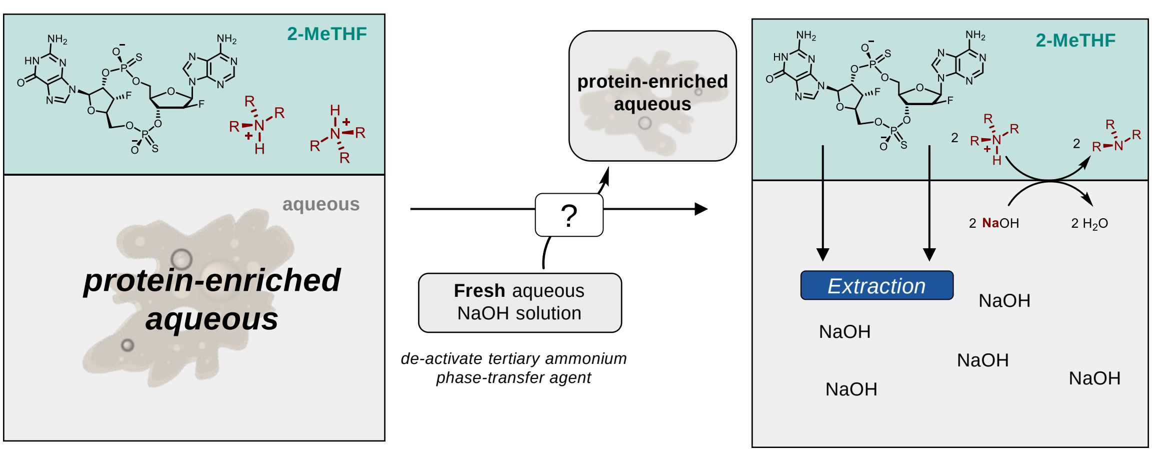
78

Intercepting an Aqueous Crystallization: Back-Extraction into Water



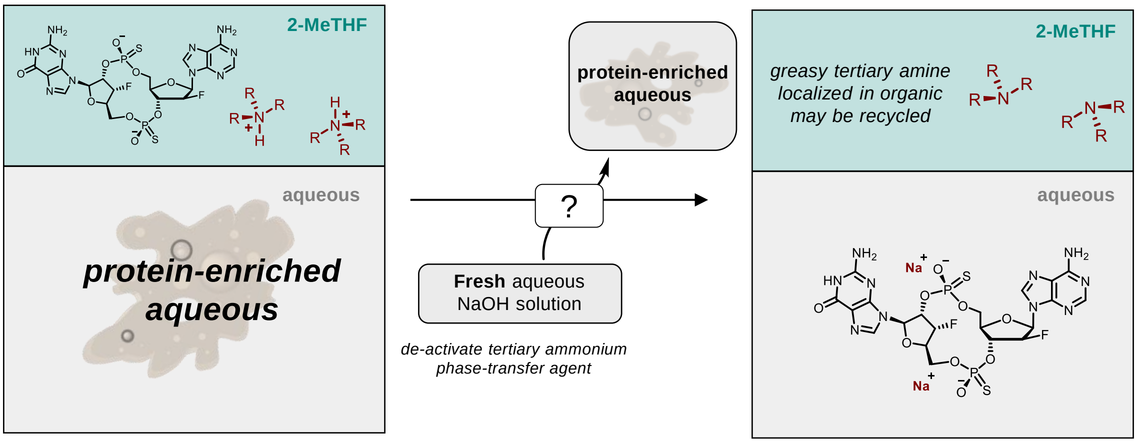
79

Tertiary Amines as pH-Switchable Extractants?



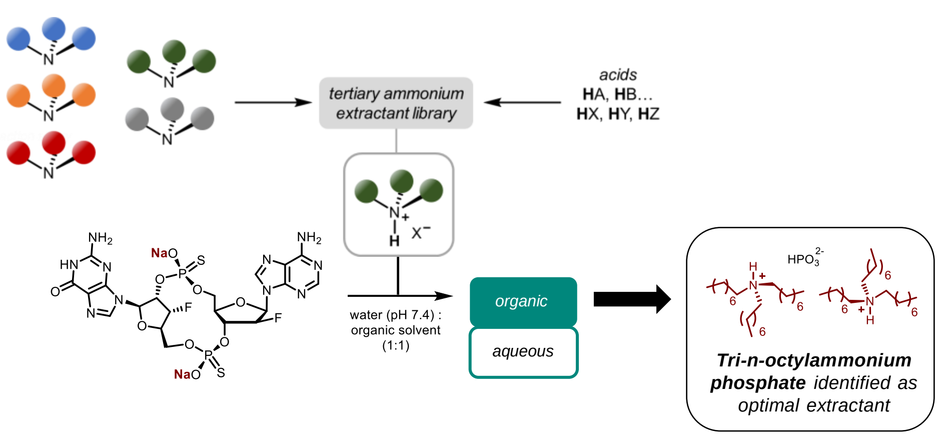
80

Hypothesis: Tertiary Amines as pH-Switchable Extractants



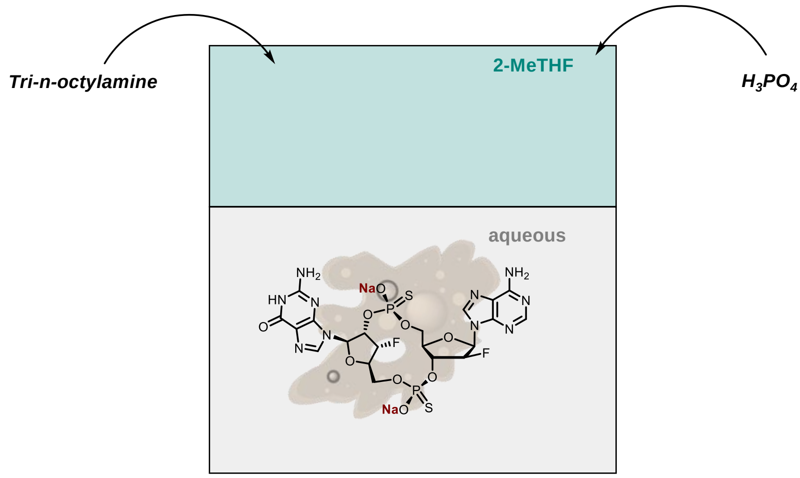
High-Throughput Discovery of Tertiary Ammonium Extractants

Extractant library synthesized by combinatorial acid / base reactions

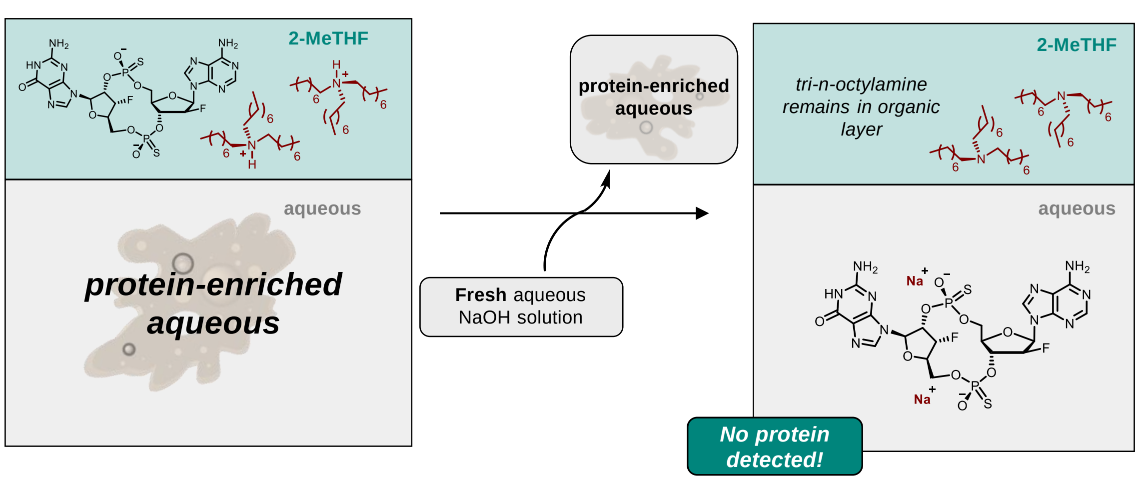


Winston, M. S. *et al. Org. Process Res. Dev.* **2023**, *27*, 179.

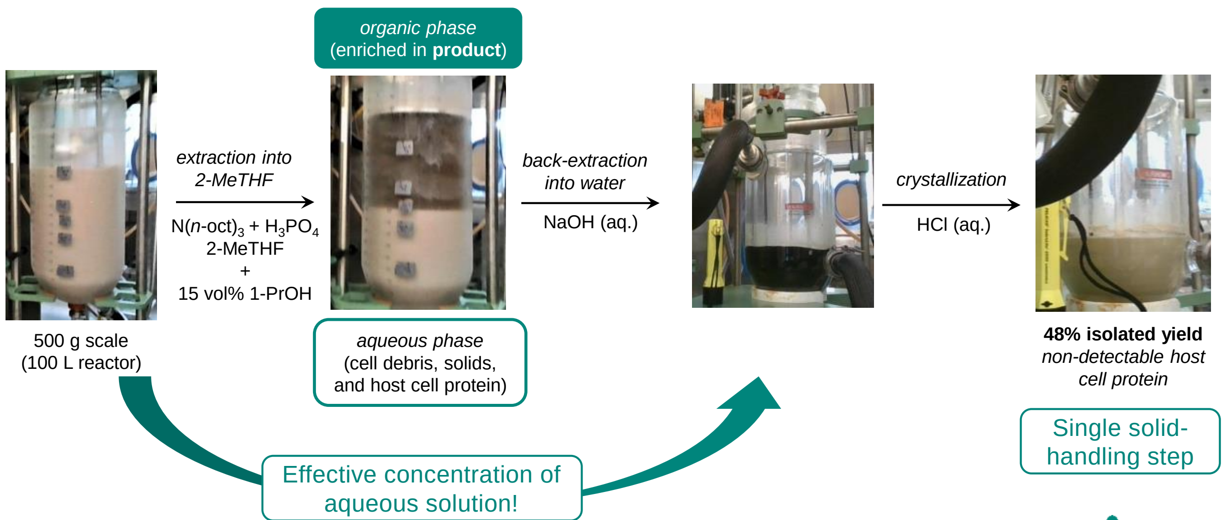
pH-Switchable Extractants: Proof-of-Concept Achieved!



pH-Switchable Extractants: Proof-of-Concept Achieved!

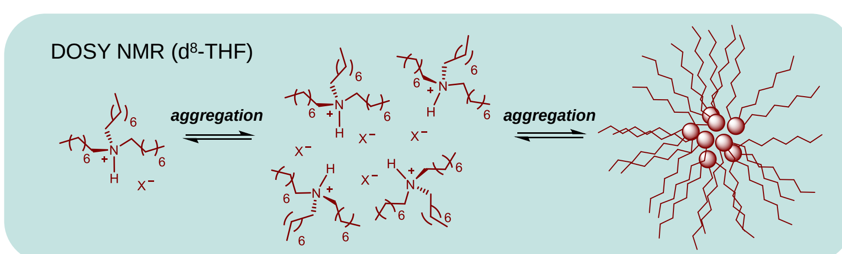


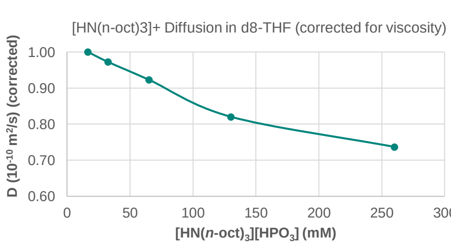
Prep Scale Demonstration of Extraction

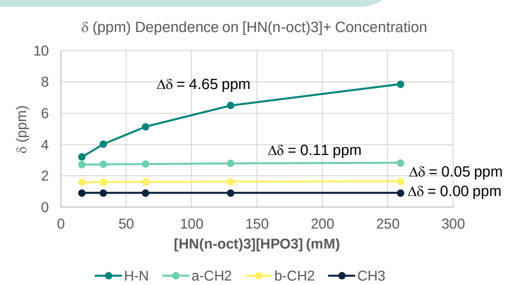


85

Probing Solution-State Extractant Interactions

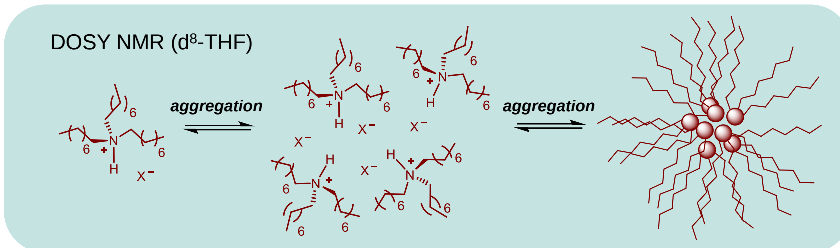






86

Probing Solution-State Extractant Interactions



MK-1454 likely extracted in reverse micelles

General phenomenon demonstrated with other polar hydrophilic molecules

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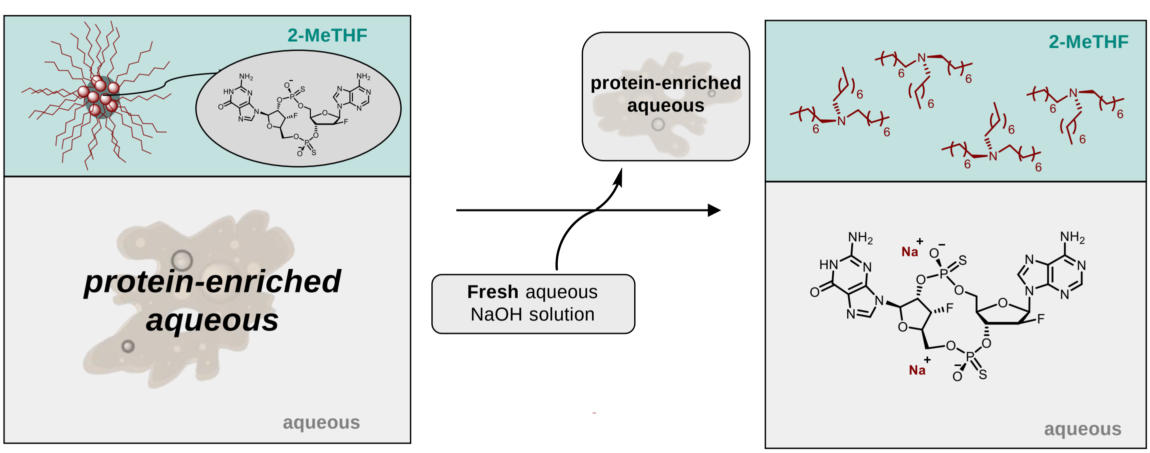
87

Reverse Micellization of pH-Switchable Extractants



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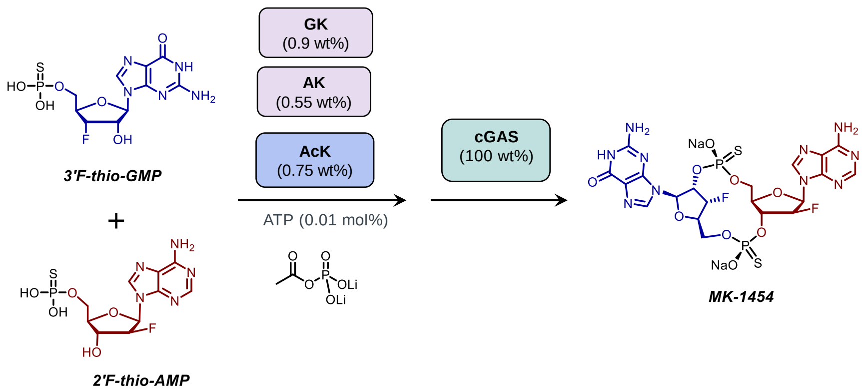
88

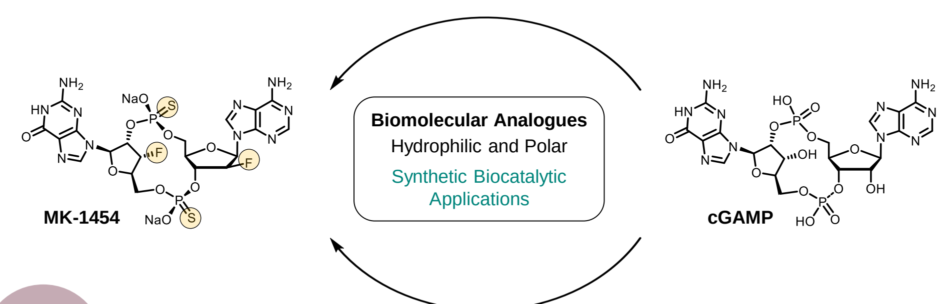
Summary and Lessons Learned



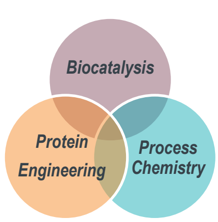
- **Enzyme engineering** in concert with process development enabled a complex biocatalytic cascade to MK-1454.
- Leveraged **enzyme substrate specificity** and **diastereoselectivity** to prepare a single cyclic dinucleotide diastereomer.
- >10x improvement in **process mass intensity** (~800) over 1st generation non-biocatalytic route.

Summary and Lessons Learned

***Function** inspires medicinal chemists*

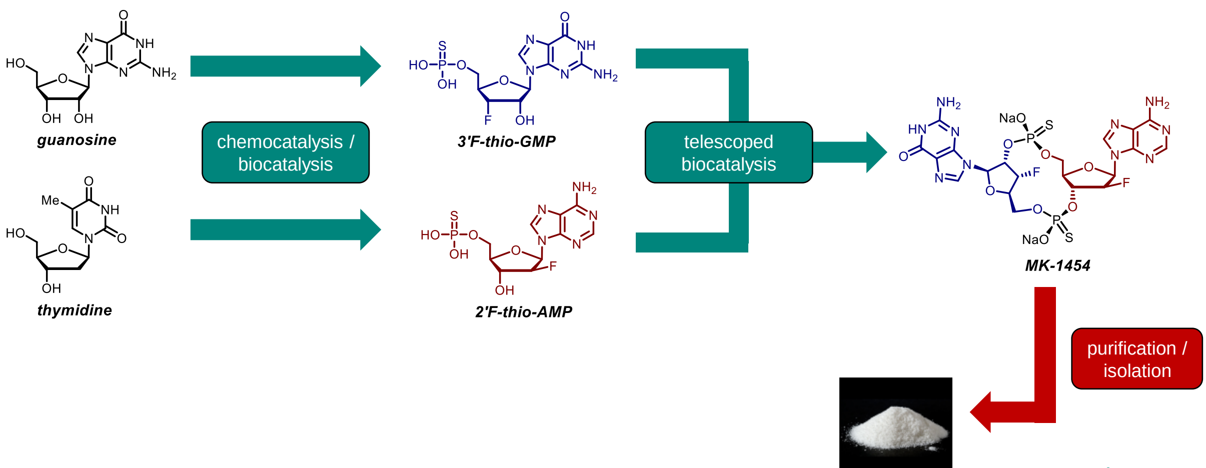


***Biosynthesis** inspires process chemists*



Advances in biocatalysis necessitate novel process chemistry solutions

Overview of MK-1454 Commercial Manufacturing Route



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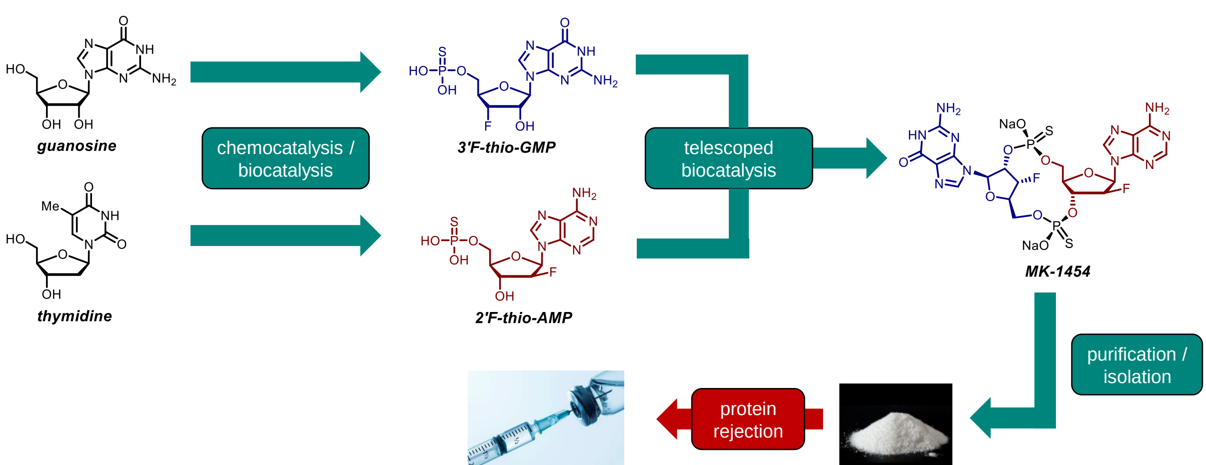
91

Overview of MK-1454 Commercial Manufacturing Route



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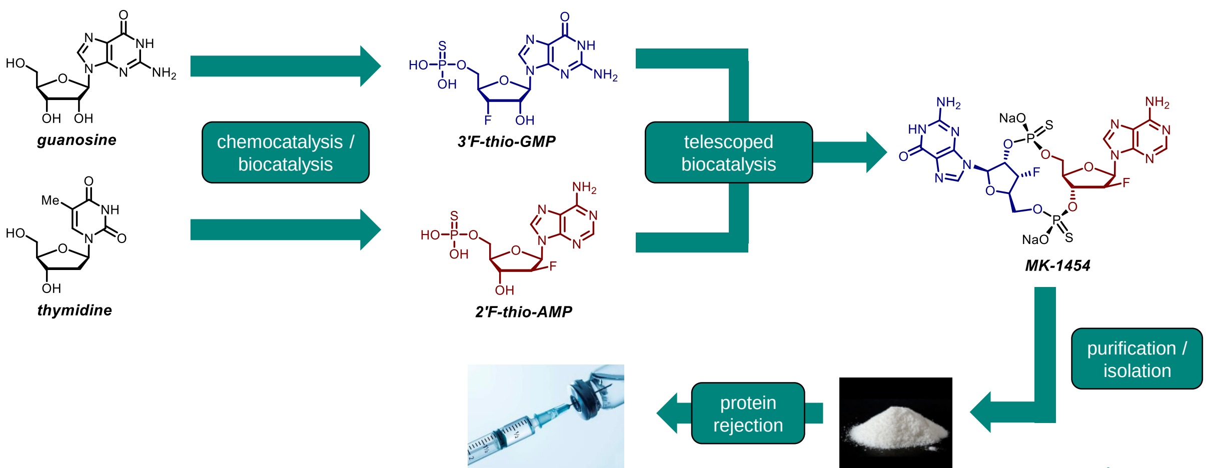
92

Overview of MK-1454 Commercial Manufacturing Route



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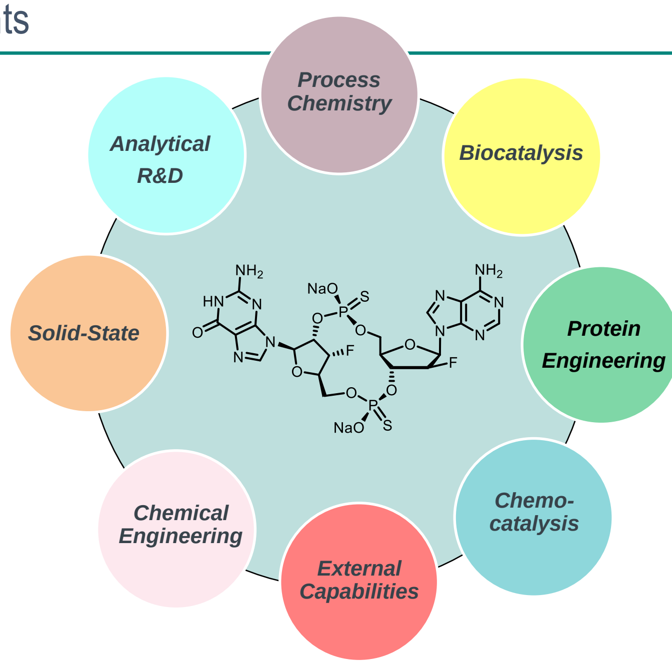
93

Acknowledgements



MERCK 94

94

Acknowledgements

Amanda Makarewicz
Andrew Neel
Artis Klapars
Becky Ruck
Ben Sherry
Ben Turnbull
Bill Morris
Birgit Kosjek
Brittany Kassim
Cheol Chung
Chihui An
Colin Lam
Dani Schultz
Daniel Zewge
David Lamberto
Deeptak Verma
Dewan Andrews
Dorothy Levorse
Emily Corcoran
Beth Fisher
Eric Phillips
Erik Guetschow
Erik Regalado
Feng Peng
Fuh-Rong Tsay
Greg Hughes
Guy Humphrey
Hongming Li
Jacob Forstater
Jeff Moore
Jake Song
Jake Waldman
Jason Kowalski
Jenna Terebetski
Jenny Obligacion
Ji Qi
Jim Corry
Jimmy DaSilva
Jinchu Liu
Jing Su
JJ Yin
John Limanto
John McIntosh
Joseph Smith
Josh Bader
Justin Newman
Keith Canada
Kerstin Zawatzky
Kevin Sirk
Leo Joyce
Lisa Frey
Lucy Kwan
Lushi Tan
Marc Poirier
Mark Huffman
Mark Weisel
Matt Maddess
Matthew Winston
Michael Pirnot
Mikhail Reibarkh
Mona Larsen
Nara Variankaval
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Patrick Fier
Paul Devine
Fengqiang Wang
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Stephanus Axnanda
Steve Castro
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Tamas Benkovics
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Tim Wright
Travis Armiger
Tyler Davis
Vito Rapisardi
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Yi Ning Ji Chen
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95

95

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96

96


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