



# Striving Toward Greener Chemistry in the Pharma Industry: the Role of the ACS Pharmaceutical Roundtable

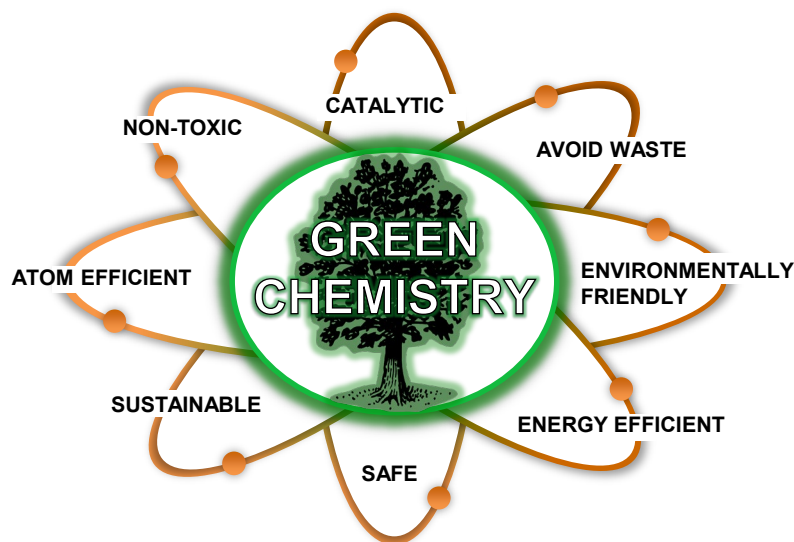
*Timothy D. White*

*22<sup>nd</sup> Annual Pollution Prevention Conference  
Indianapolis, IN, September 18, 2019*

# Green Chemistry

**Green Chemistry** and sustainable science is the strategic design, development, and implementation of chemical products and processes that reduce or eliminate the use and generation of hazardous substances and waste, are inherently safe, and increase efficiency while minimizing environmental footprint and impact.

**Good science** is the key to sustainability, green chemistry, and low cost manufacturing across the globe.



**Noyori** - "...green chemistry is not just a catchphrase. It is an indispensable principle of chemical research that will sustain our civilized society in the twenty-first century and further into the future."<sup>\*1</sup>





**Tucker** - "...a privileged opportunity for innovation" representing "an emerging new frontier of exploration."<sup>\*2</sup>

If industry focuses on developing the best chemistry, then almost always this leads to the lowest costs and greenest processes.

<sup>\*1</sup> Noyori, R. "Synthesizing our future." *Nature Chemistry* **2009**, 1, 5-6.

<sup>\*2</sup> Tucker, J.L. "Green Chemistry, a Pharmaceutical Perspective." *Org. Process Res. Dev.* **2006**, 10(2), 315-319.

# Business Case for Green Chemistry

-  pharmaceutical & generics industries may produce  $\geq 100$  million kg APIs per year <sup>\*1</sup>
-  cEF  $\geq 150$  kg waste per kg API ( $> 99.3\%$ )  $\rightarrow \geq 15$  billion kg of co-produced waste
-  annual waste disposal cost of  $\sim \$30$  billion 

**opportunity** for industry to utilize **green chemistry** to trim both process inputs and waste, and **create \$ billions in economic, environmental, and social value**



*Pharmaceutical Development Timelines*



**METRICS are vital**

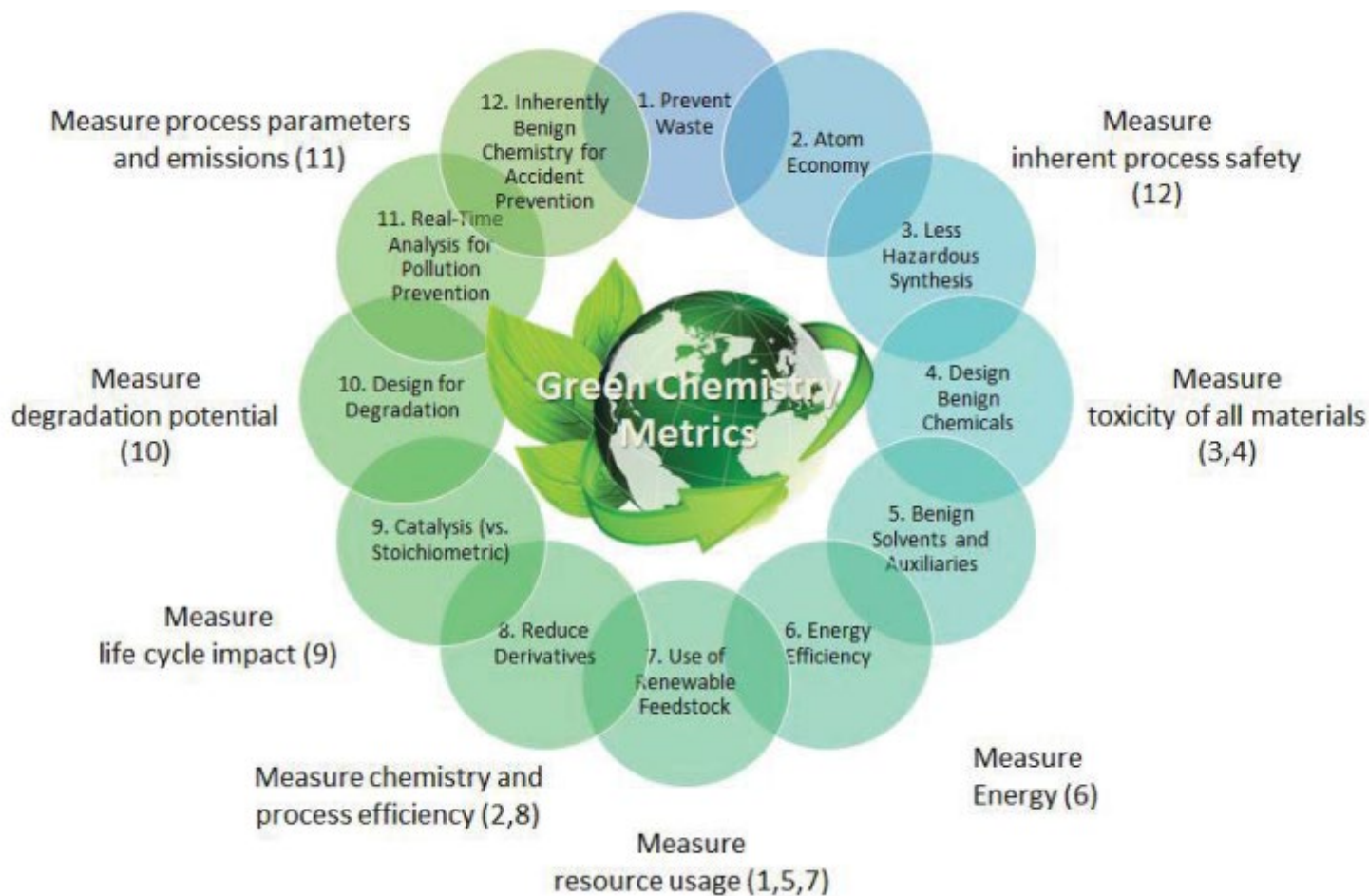


**“you can’t manage what you don’t measure”**



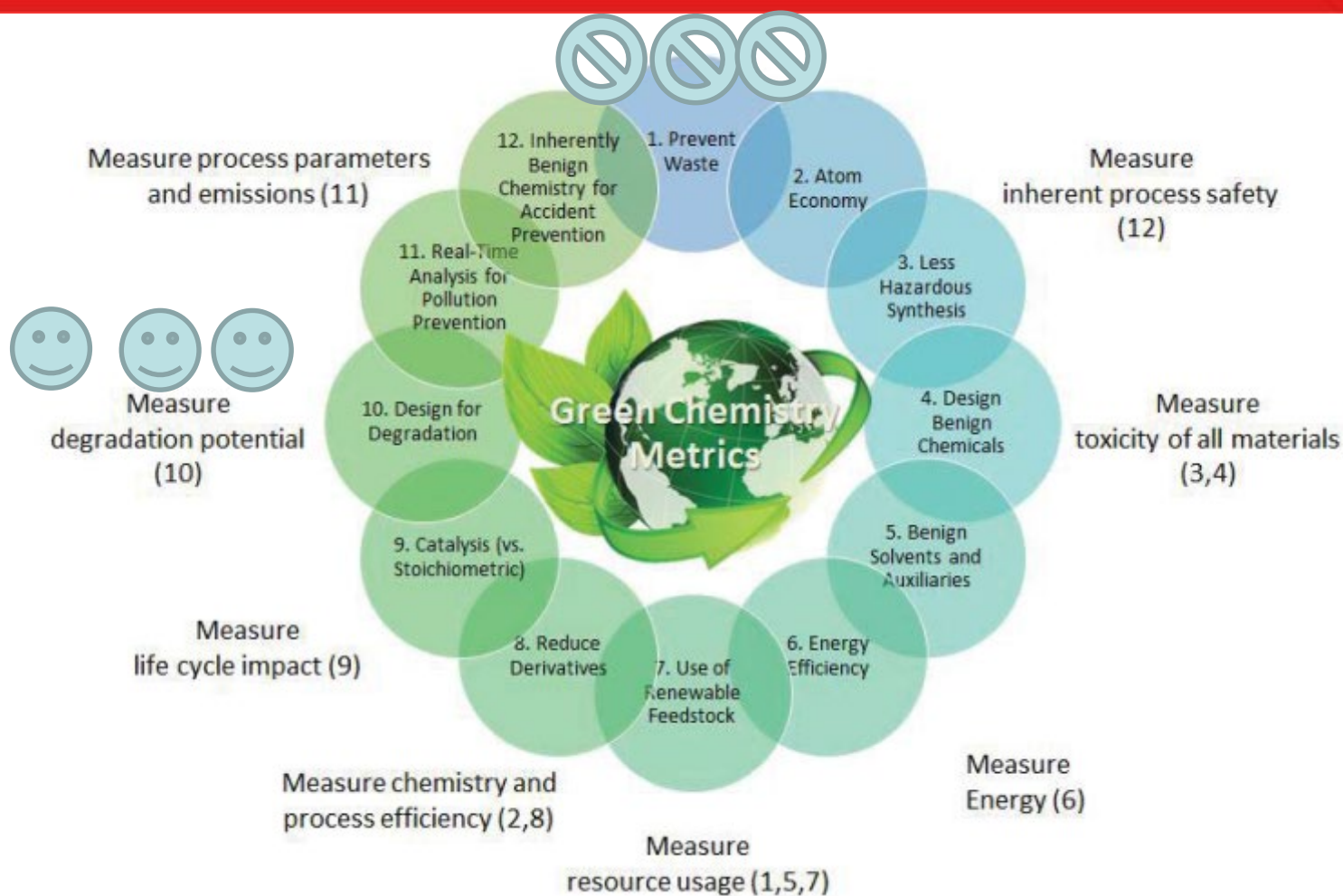
<sup>\*1</sup> B. W. Cue, (2012) Green Chemistry Strategies for Medicinal Chemists, in Green Techniques for Organic Synthesis and Medicinal Chemistry (eds. Zhang, W., and Cue, B. W.). John Wiley & Sons, Chichester, UK.

# 12 Principles of Green Chemistry



P. T. Anastas & J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press: New York, 1998.

# 12 Principles of Green Peptides



P. T. Anastas & J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press: New York, 1998.

# 2019 ACS Pharmaceutical Roundtable



## Tools for Innovation in Chemistry

Solvent Selection  
Reagent Guides  
PMI-LCA & PMI Prediction  
MedChem Tips & Tricks



## Advancing Research

Key Research Areas  
Research Grants  
Journal Publications  
Impact



## Educating Leaders

Chem21  
Training Workshops  
Presentations  
Awards



## Global Collaboration

India  
China  
PSCI & IQ  
Benchmarking

## Current Members

AbbVie  
Amgen  
AstraZeneca  
Bayer  
Biogen  
Boehringer Ingelheim  
Bristol-Myers Squibb  
Eli Lilly and Company  
F. Hoffmann-La Roche Ltd.  
Gilead  
GlaxoSmithKline  
Ipsen  
Johnson & Johnson  
Merck & Co., Inc  
Neurocrine  
Novartis  
Novo Nordisk  
Pfizer, Inc.  
Sanofi  
Takeda  
Vertex  
ACS Green Chemistry  
Institute®

- Pre- Competitive Consortium Founded in 2005 by Merck, Lilly and Pfizer
- Catalyze the integration of green chemistry and engineering in the pharmaceutical industry

<https://www.acsgcipr.org/>



# 2019 ACS Pharmaceutical Roundtable

## Members

22

as of 31 December 2018



## Associates & Affiliates

6



## New Members



as of 28 February 2019

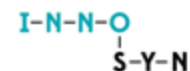


(Affiliate)

## Prospectives

BACHEM

Hovione



# Pharma Roundtable Priorities

- \*2007 KRA Manuscript: *Green Chem.*, 2007,9, 411-420

## Key green chemistry research areas—a perspective from pharmaceutical manufacturers

David J. C. Constable,<sup>a</sup> Peter J. Dunn,<sup>\*b</sup> John D. Hayler,<sup>c</sup> Guy R. Humphrey,<sup>d</sup> Johnnie L. Leazer, Jr.,<sup>d</sup> Russell J. Linderman,<sup>e</sup> Kurt Lorenz,<sup>f</sup> Julie Manley,<sup>g</sup> Bruce A. Pearlman,<sup>h</sup> Andrew Wells,<sup>i</sup> Aleksey Zaks<sup>h</sup> and Tony Y. Zhang<sup>f</sup>

Received 7th March 2007, Accepted 26th March 2007

First published as an Advance Article on the web 17th April 2007

DOI: 10.1039/b703488c

753 Citations

In 2005, the ACS Green Chemistry Institute (GCI) and the global pharmaceutical corporations developed the ACS GCI Pharmaceutical Roundtable to encourage the integration of green chemistry and green engineering into the pharmaceutical industry. The Roundtable has developed a list of key research areas. The purpose of this perspective is to summarise how that list was agreed, provide an assessment of the current state of the art in those areas and to highlight areas for future improvement.

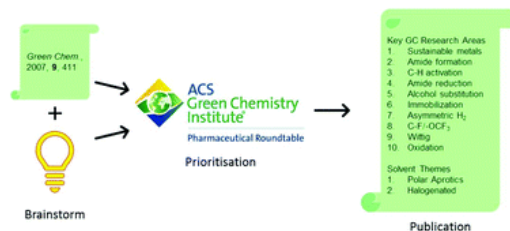
- 2018 KRA Manuscript: *Green Chem.*, 2018,20, 5082-5103.

## Key Green Chemistry research areas from a pharmaceutical manufacturers' perspective revisited



[Marian C. Bryan](#),<sup>a</sup> [Peter J. Dunn](#),<sup>b</sup> [David Entwistle](#),<sup>c</sup> [Fabrice Gallou](#),<sup>d</sup> [Stefan G. Koenig](#),<sup>e</sup> [John D. Hayler](#),<sup>\*f</sup> [Matthew R. Hickey](#),<sup>\*g</sup> [Shaun Hughes](#),<sup>h</sup> [Michael E. Kopach](#),<sup>i</sup> [Gerard Moine](#),<sup>j</sup> [Paul Richardson](#),<sup>k</sup> [Frank Roschangar](#),<sup>l</sup> [Alan Steven](#)<sup>h</sup> and [Franz J. Weiberth](#)<sup>m</sup>

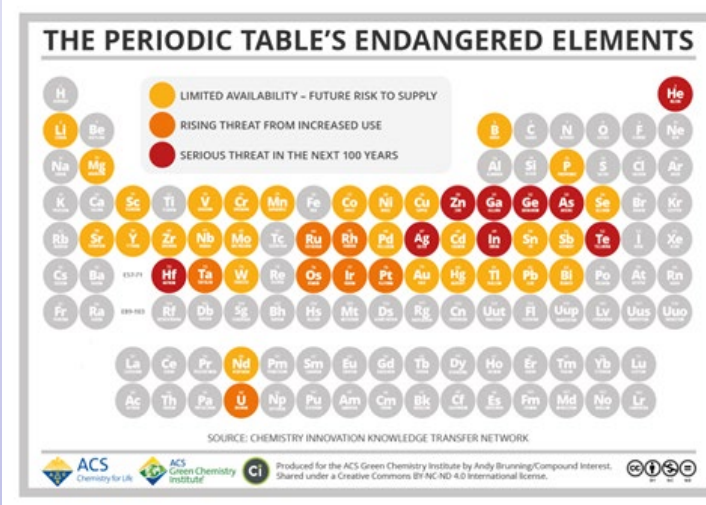
⊕ Author affiliations





# Overview: Pharma Key Research Areas

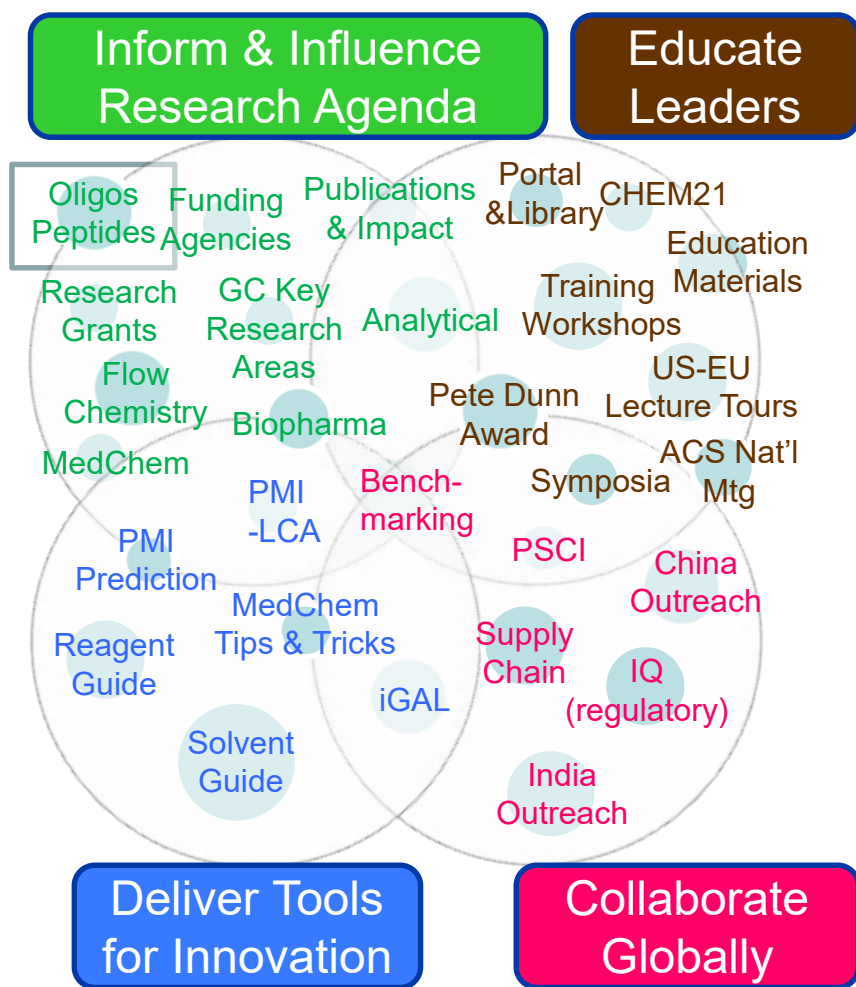
- Inexpensive / **sustainable metals** methodologies
- Sustainable catalysis for (direct) **amide or peptide formation**
- **Green oxidants** aliphatic and aromatic **C–H activation**
- **Amide reductions** avoiding  $\text{LiAlH}_4$  and diborane.
- Direct **substitution of alcohols**
- **Catalyst immobilization** (no loss of kinetics)
- **Asymmetric hydrogenation** of unfunctionalized olefins/ enamines/imines
- Improved **fluorination/trifluoromethoxylation**
- **Wittig** chemistry without  $\text{Ph}_3\text{PO}$ .
- **Alternatives for oxidations**, C–O or C–N redox processes
- **Polar aprotic solvents** replacements
- **Halogenated solvents** replacements



## Grant's Program: 2019 New RFP's!

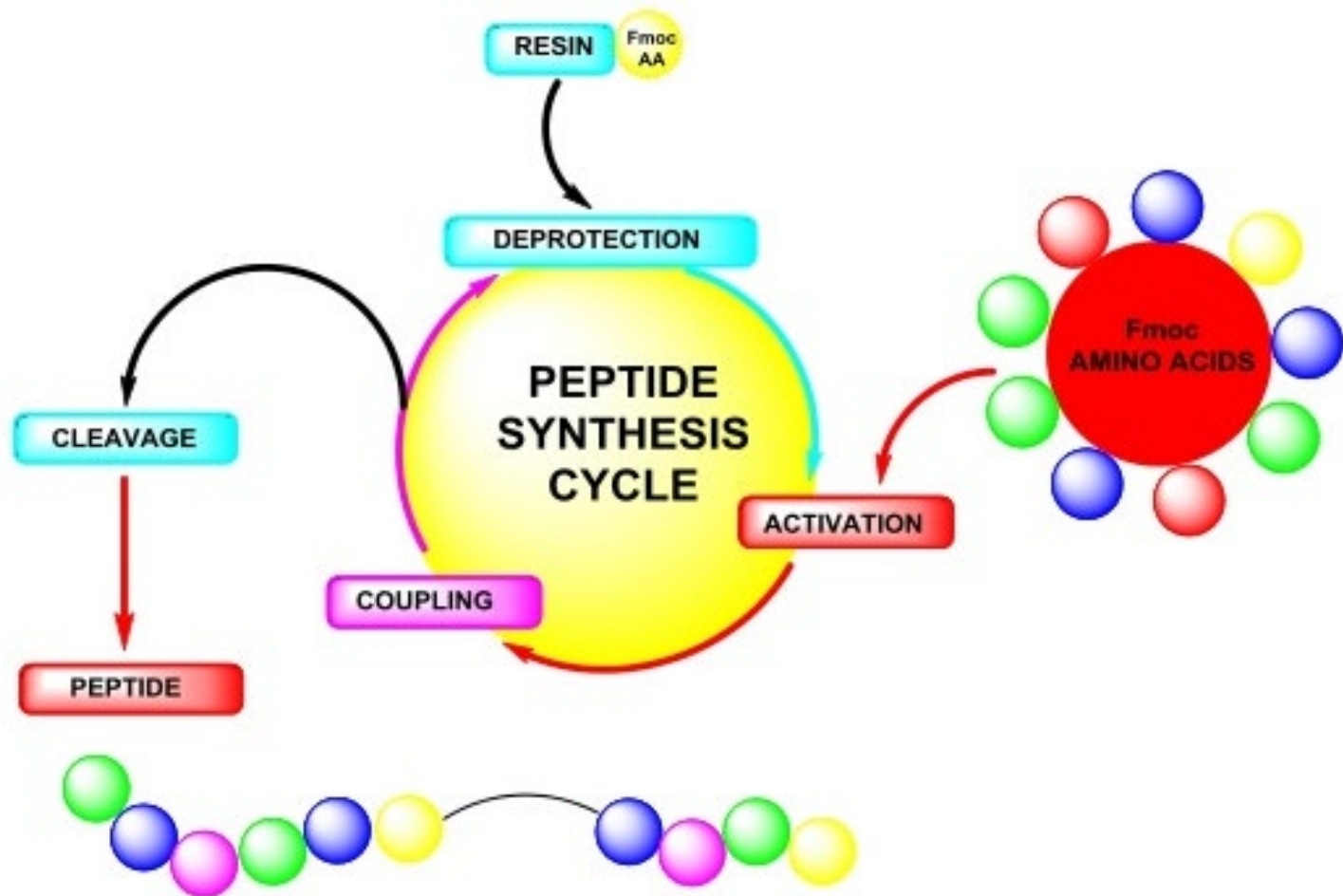
- Ignition grants (\$25K)
- Non-metal catalysis cross-coupling rxns (\$50K)

# Pharma RT 2025 Strategic Priorities



- Peptides and Oligos Relatively New Team founded in 2016
- Charter: To educate and influence today's and tomorrow's scientists and industries in the business value and scientific merit to utilize green chemistry and engineering principles to guide development and manufacture of peptide, oligonucleotide products.

# Solid Phase Peptide Synthesis (SPPS)



# Solid Phase Peptide Synthesis

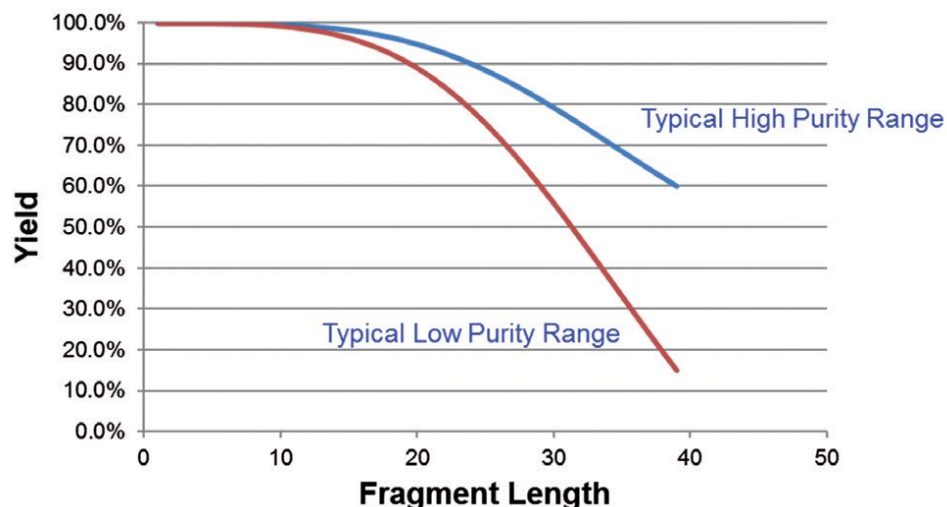
## Advantages:

- ✓ Proven technology
- ✓ Efficient method of production for short sequences
- ✓ Accepted current practice

## Challenges:

- ✓ Solvent intensive process
- ✓ Yield and purity significantly decrease as peptide length increases
- ✓ Addition and deletion (and analog) impurities are possible and propagate
- ✓ Up to 20% risk of total loss increases as a function of peptide length\*

Yield versus Fragment Length Assumption

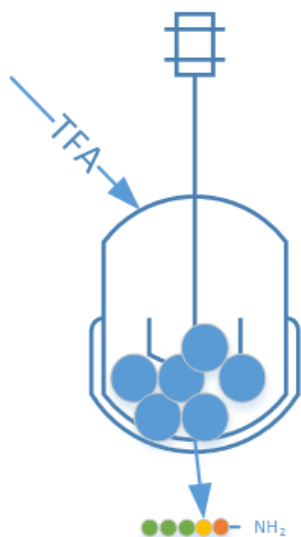


Source: \*Sustainability Challenges in Peptide Synthesis and Purification: From R&D to Production, J. Org. Chem., Article ASAP DOI: 10.1021/acs.joc.8b03001

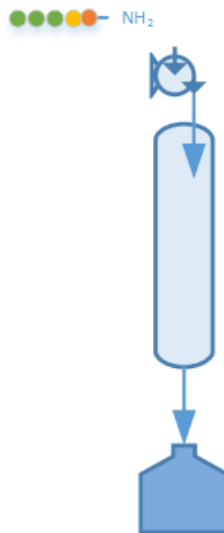
# Common Peptide Industrial Practices



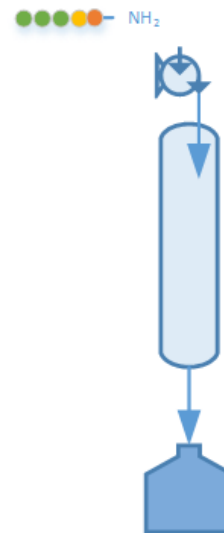
**SPPS (linear)**  
Fmoc-AA chemistry  
>3 eq AA and reagents  
DMF and NMP



**Cleavage and deprotection**  
TFA or HF  
DCM, EDC, IPE



**Reverse Phase Chromatography**  
RP Resin / ACN  
Dilute, multiple passes



**Ion Exchange Chromatography**  
RP Resin / Alcohol  
Concentration, salt exchange

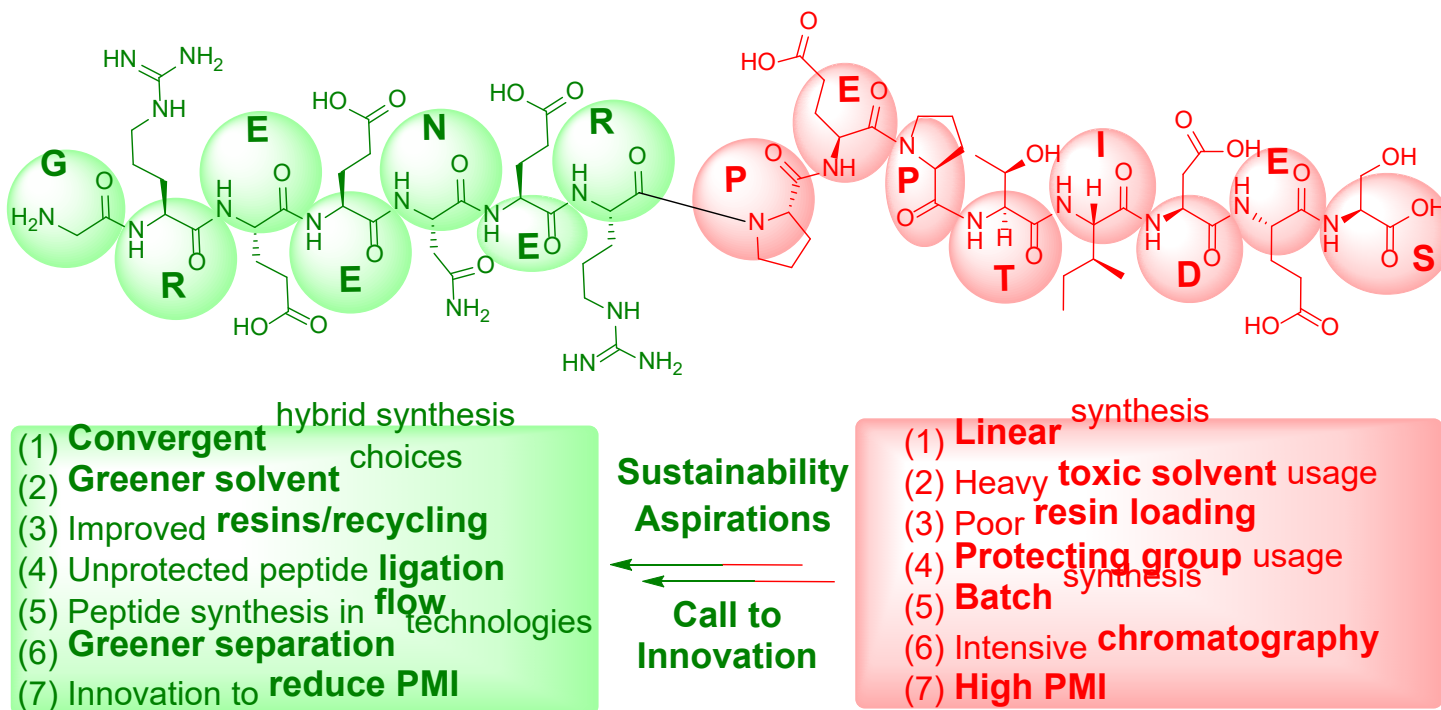


**Isolation**  
Lyophilization ( $\geq 80\%$ )  
Precip  
Spray Dry

# Pharma RT Peptide Key Research Areas

## Sustainability challenges in peptide synthesis and purification: from R&D to production

Albert Isidro-Llobet,<sup>\*a</sup> Martin N. Kenworthy,<sup>b</sup> Subha Mukherjee,<sup>c</sup> Michael E. Kopach,<sup>d</sup>  
Katarzyna Wegner,<sup>e</sup> Fabrice Gallou,<sup>f</sup> Austin G. Smith,<sup>g</sup> Frank Roschangar<sup>h</sup>



*J. Org. Chem.*, **2019**, 84 (8), pp 4615–4628



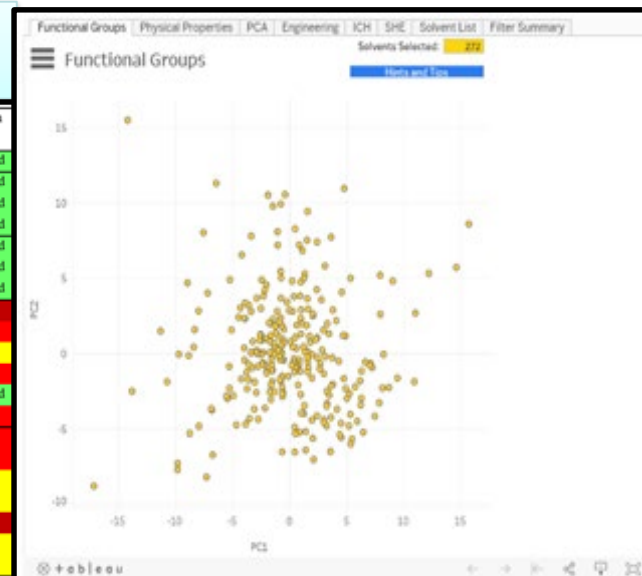
# Tools to Make Processes Greener

## Solvent Guides/Interactive Tool

**Guides:** 77 solvents;  
3 criteria: safety,  
health, environment

**Interactive Tool:** 272  
solvents/ selection  
based on physical  
properties, functional  
groups and  
environmental data.

Family	Solvent	BP (°C)	FP (°C)	Worst H <sub>500</sub>	H <sub>500</sub>	Safety score	Health score	Env. score	Ranking by default	Ranking from the survey
Water	Water	100	na	none	none	1	1	1	Recommended	Recommended
Alcohols	EtOH	78	13	H319	none	4	3	3	Recommended	Recommended
	i-PrOH	82	12	H319	none	4	3	3	Recommended	Recommended
	n-BuOH	118	29	H318	none	3	4	3	Recommended	Recommended
Esters	Ethyl acetate	77	-4	H319	none	5	3	3	Recommended	Recommended
	i-PrOAc	89	2	H319	none	4	2	3	Recommended	Recommended
	n-BuOAc	126	22	H336	none	4	2	3	Recommended	Recommended
Ethers	Diethyl ether	34	-45	H302	none	10	3	7	Hazardous	HH
	Diisopropyl ether	69	-28	H336	none	9	3	5	Hazardous	Hazardous
	Me-THF	80	-11	H318	none	6	5	3	Problematic	Problematic
	1,4-Dioxane	101	12	H351	none	7	6	3	Problematic	Hazardous
	Anisole	154	52	none	none	4	1	5	Problematic	Recommended
	DME	85	-6	H360	none	7	9	3	Hazardous	Hazardous
Hydrocarbons	Pentane	36	-40	H304	H411	8	3	7	Hazardous	Hazardous
	Hexane	69	-22	H361	H411	8	7	7	Hazardous	Hazardous
	Heptane	98	-4	H304	H410	6	2	7	Problematic	Problematic
	Me-Cyclohexane	101	-4	H304	H411	6	2	7	Problematic	Problematic
	Benzene	80	-11	H350	none	6	10	3	Hazardous	HH
	Toluene	111	4	H351	none	5	6	3	Problematic	Problematic
	Xylenes	140	27	H312	none	4	2	5	Problematic	Problematic



## Reagent Guides: reagentguides.com

18 guides, > 150  
reagents, citation  
links

**Coming soon!** Amide  
bond reagent guide  
specific to  
polypeptides

The reagent guides purpose is to encourage chemists to choose a 'greener' choice of reaction conditions. The guides aim to achieve this by providing transparency through the use of Venn diagrams in addition to improving understanding by discussion and up to date references.

The Reagent Guides

Select the chemical transformation of interest.

[VIEW >](#)

How to Interpret the Venn Diagrams

[VIEW >](#)

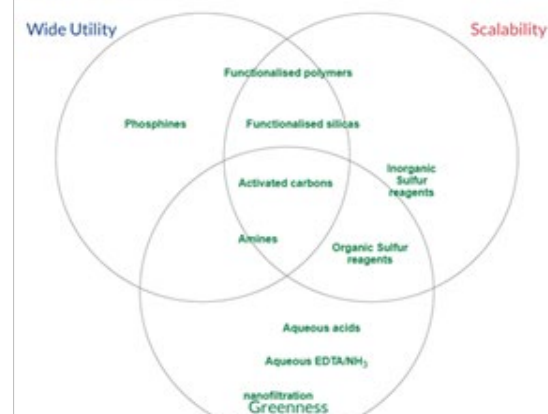
Ethos of the Reagent Guides

Understand the purpose behind the construction of the guides.

[VIEW >](#)

Home / Reagent Guides / Metals Removal / Venn Diagram

### Venn Diagram



# Pharmaceutical Roundtable Metrics



## Process Mass Intensity Metric



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

Where:

**Process** is all steps of a synthetic path from commonly available materials to the final bulk active pharmaceutical ingredient ("API")

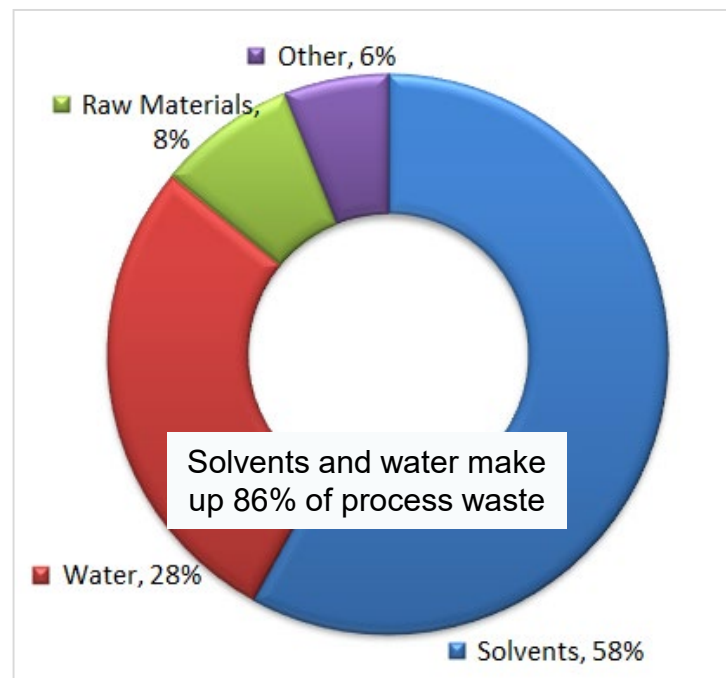
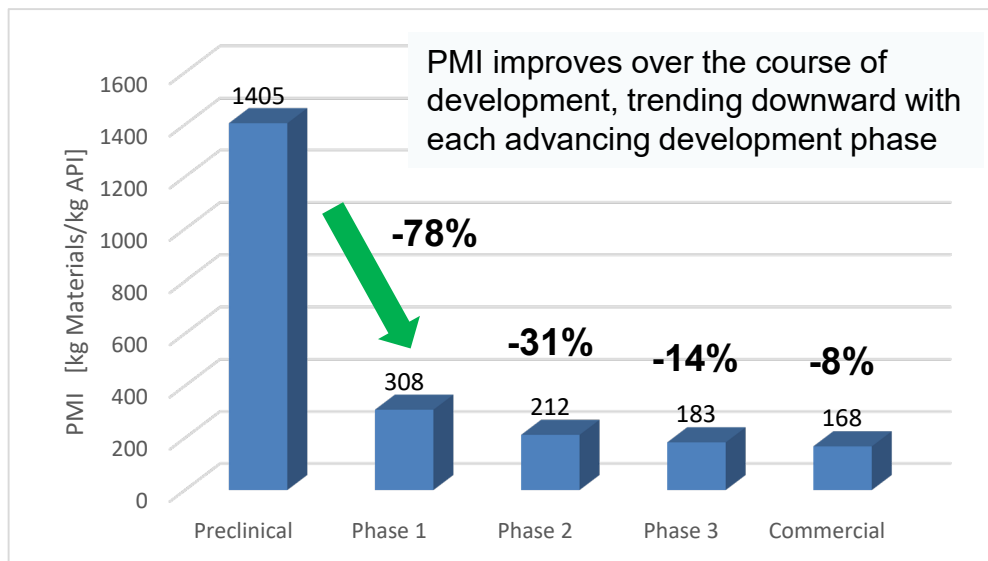
**Raw Materials** are all materials including water that are used directly in the process of synthesizing, isolating, and purifying the API salt

**Bulk API out** is the final salt form of the active ingredient that was produced in the synthesis, dried to the expected specification

Jimenez-Gonzalez, C. *et al. Org. Process Res. Dev.* **2011**, 15, 912–917.

# Process Mass Intensity (PMI)

ACS GCI compiled industry waste data for pharmaceutical manufacturing across development and commercial in 2007 and 2008\*1-3



ACS GCI PR availed free  
Excel PMI calculator\*2

\*1 R. K. Henderson, J. Kindervater and J. B. Manley, *Lessons Learned Through Measuring Green Chemistry Performance – The Pharmaceutical Experience* (2007).

\*2 ACS GCI Pharmaceutical Roundtable presentation “Convergent PMI Calculator” (2014).

\*3 The PMI data, which exclude solvent and water-intensive biopharmaceutical fermentation processes, were significantly higher in 2008 compared to 2007, possibly due to reassessment of synthesis starting points. We show the 2008 data.

# Peptide Research Grant: Professor Jennifer Stockdill

## Bringing Macrolactamization Full Circle: Self-Cleaving Head-to-Tail Macrocyclization of Unprotected Peptides via Mild *N*-Acyl Urea Activation

Christine A. Arbour,<sup>a</sup> Kayla J. Belavek,<sup>a</sup> Rooha Tariq,<sup>a</sup> Subha Mukherjee,<sup>b</sup> Janine K. Tom,<sup>c</sup> Albert Isidro-Llobet,<sup>d</sup> Michael E. Kopach,<sup>e</sup> and Jennifer L. Stockdill<sup>\*a</sup>

<sup>a</sup>Department of Chemistry, Wayne State University, Detroit, MI, USA 48202

<sup>b</sup>Bristol-Myers Squibb, Chemical and Synthetic Development, New Brunswick, NJ, 08903, USA

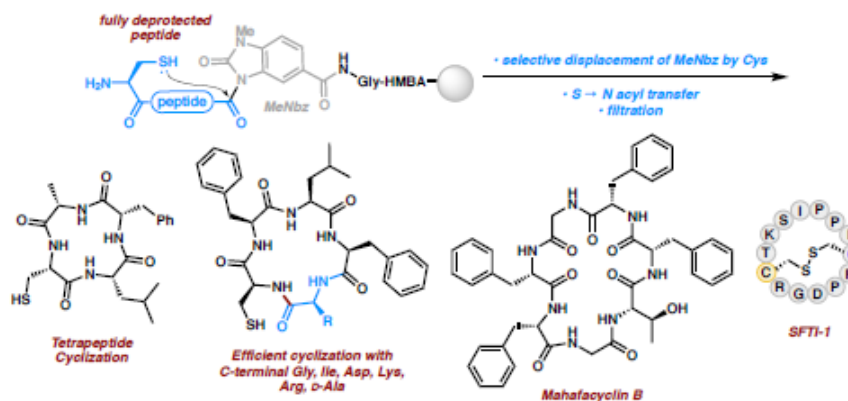
<sup>c</sup>Amgen, Inc.

<sup>d</sup>GlaxoSmithKline, Medicines Research Centre, Stevenage SG1 2NY, UK

<sup>e</sup>Eli Lilly and Company, Indianapolis, IN, 46285, USA

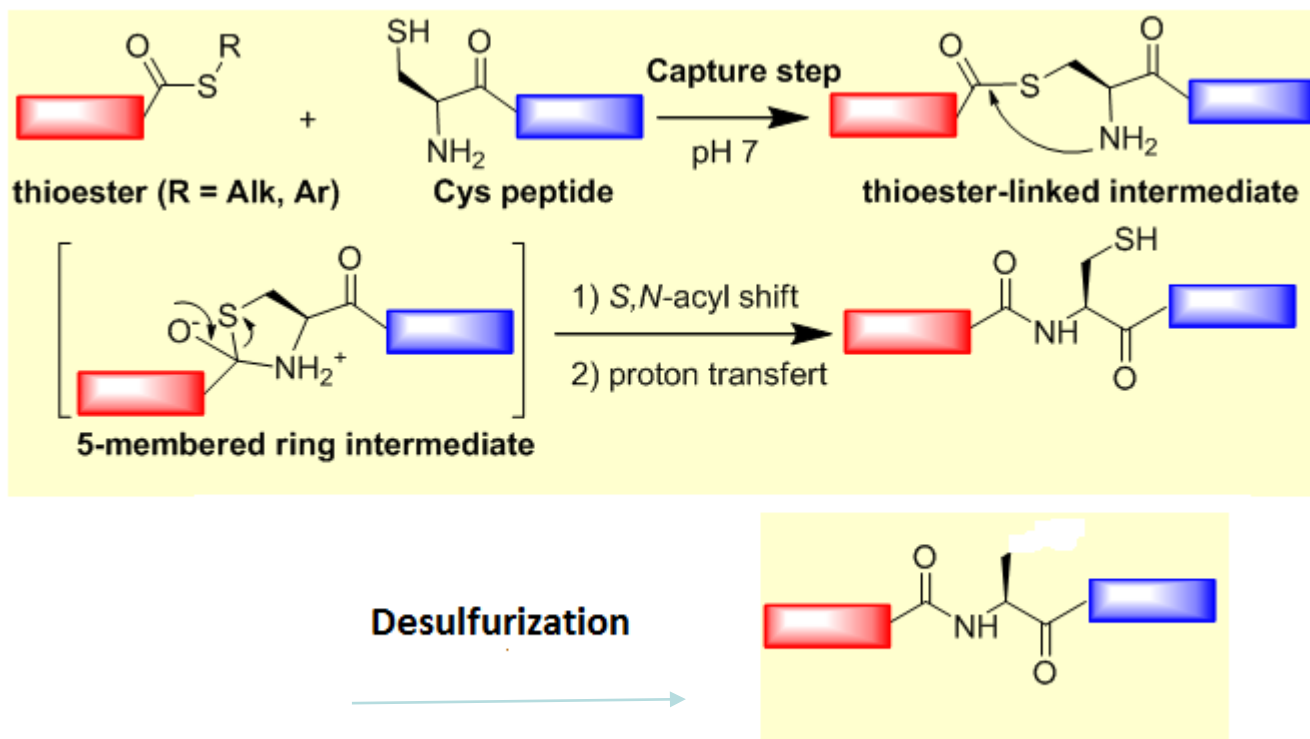
*Supporting Information Placeholder*

**ABSTRACT:** We establish herein conditions for the efficient self-cleaving cyclization of unprotected *N*-acyl urea-linked peptides to form head-to-tail macrocyclic peptides mediated by *N*-terminal cysteine. We report a detailed investigation of the parameters of the reaction, including variation of the reaction conditions, the *N*-terminal residue, the *C*-terminal residue, the rinsing protocol, and the macrocycle size. Two sets of optimized conditions are employed in the synthesis of macrocyclic targets ranging from a tetrapeptide to the disulfide-linked 14-mer, sunflower trypsin inhibitor 1, and a Gly analog thereof. Under these conditions, no *C*-terminal epimerization, hydrolysis, or disulfide dimer formation is observed.



*J. Org. Chem.*, 2019, 84 (2), pp 1035–1041

# Native Chemical Ligation (NCL)



- Coupling of unprotected Peptides, potentially attractive option to Produce peptides with cysteine and alanine.
- Lack of Green Desulfurization Methodology has limited utility.
- Prof. Stockdill Awarded Roundtable Research grant extension to develop greener desulfurization methodology.



# Key 2018 Novartis Contribution

## ■ **N-Butylpyrrolidinone as Alternative Solvent for Solid-Phase Peptide Synthesis**

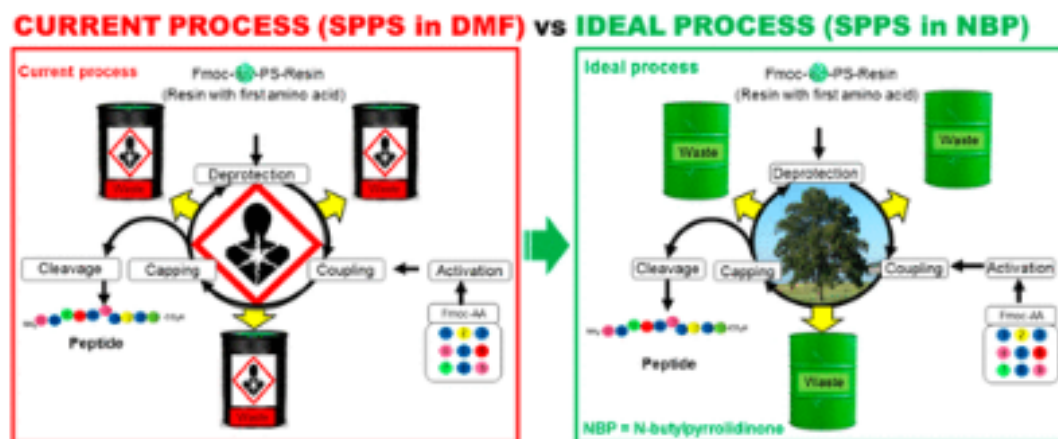
*John Lopez, Stefan Pletscher, Andreas Aemissegger, Christoph Bucher, and Fabrice Gallou*

*Org. Process Res. Dev.*, 2018, 22 (4), pp 494-503

Publication Date (Web): March 14, 2018 (Article)

DOI: 10.1021/acs.oprd.7b00389

By means of a systematic approach, several green solvent candidates were tested for their feasibility to replace the reprotoxic dimethylformamide (DMF) as a solvent used in solid-phase peptide synthesis (SPPS). According to the results presented in this ...





# ACS GCI Pharma Roundtable: Fall 2019 Meeting in China

Wednesday 18<sup>th</sup> Sept 2019: Day 1 GCIPR (**Asymchem**)

Thursday 19<sup>th</sup> Sept 2019: Day 2 GCIPR

- Onsite at Asymchem Tianjin (~100 people)
  - Roundtable meeting
  - Tour of Asymchem green chemistry capabilities

Friday 20<sup>th</sup> Sept 2019: Day 3 GCIPR (**Pharmaron**)

- Onsite at Pharmaron Beijing site (Taihe Road, BDA, Beijing 100176)
  - Roundtable meeting (~100 people)
  - Tour of Pharmaron site



# Conclusions

- Significant business case for Green chemistry and engineering in the pharmaceutical industry
- Pharmaceutical Roundtable Provides leadership and influence throughout industry and supply chain.
  - Develops valuable and powerful set of tools (e.g. solvent selection guide, PMI/LCA calculator, reagent guide, GAL manufacturing goal, PMI prediction)
  - Funds key research priorities
- ACS Pharmaceutical Roundtable has evolved its mission since 2005 from exclusive small molecule focus to include other modalities.
- Synthetic Peptide and Oligonucleotide Manufacture in largest need of innovations to improve Environmental Profile.

# Acknowledgements

## Eli Lilly and Company:

Sarah O'Keeffe

Paul Collins

Bret Huff

Brad Campbell

Shujauddin Changi

Stephen Groskreutz

Jeffrey Ferguson

Ashley Humenik

Nick Klitzig

Randy Lambertus

Allison Wolf

## ACS Pharmaceutical Roundtable:

Fabrice Gallou (Novartis)

Subha Mukherjee (BMS)

Katarzyna Wegner (Ipsen)

Martin Kenworthy (AZ)

Albert-Isidro Llobet (GSK)

Janine Tom (Amgen)

Austin Smith (Amgen)

Frank Roschangar (BI)

Isamir Martinez (GCI)