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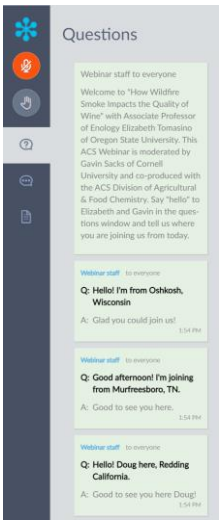

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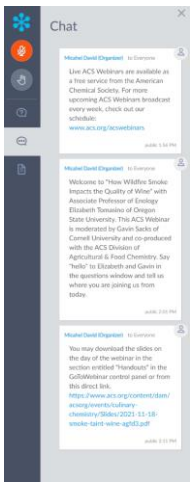

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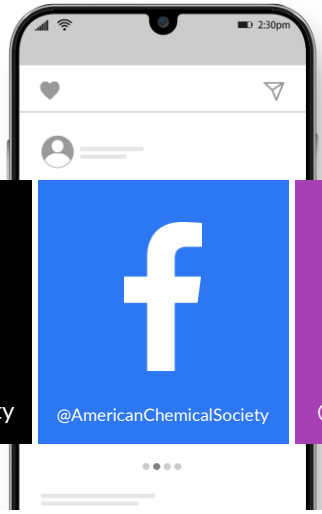

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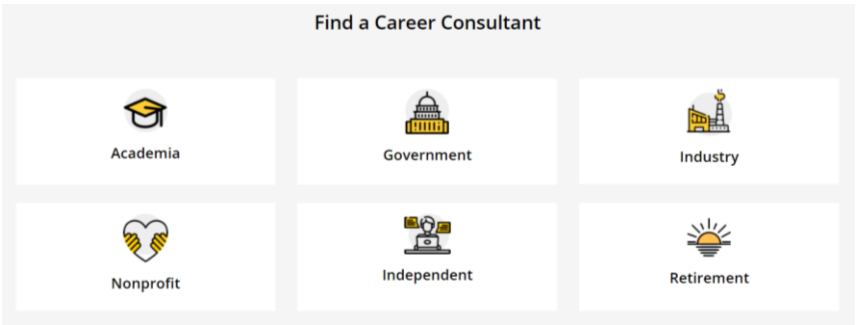

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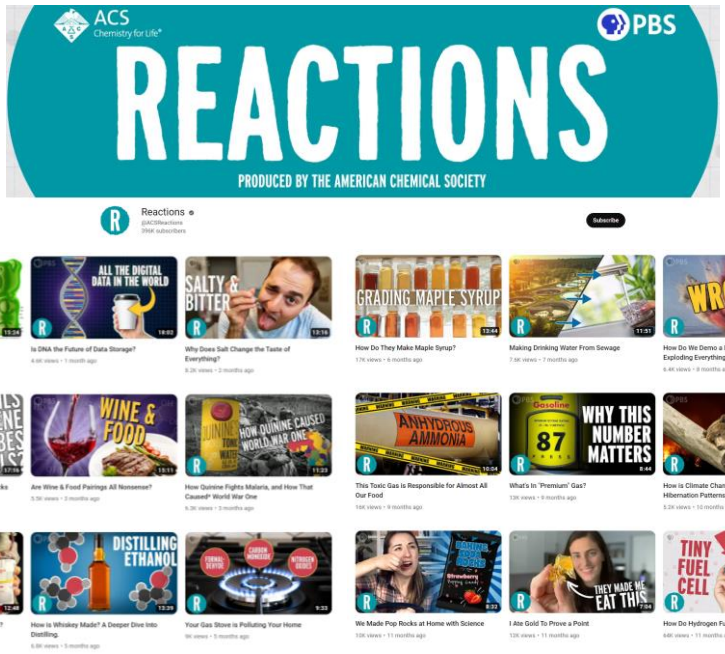

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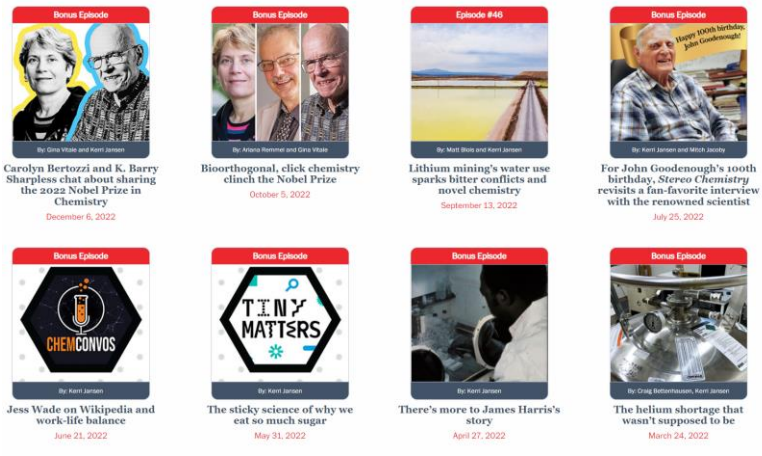

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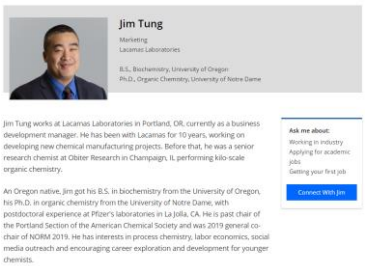

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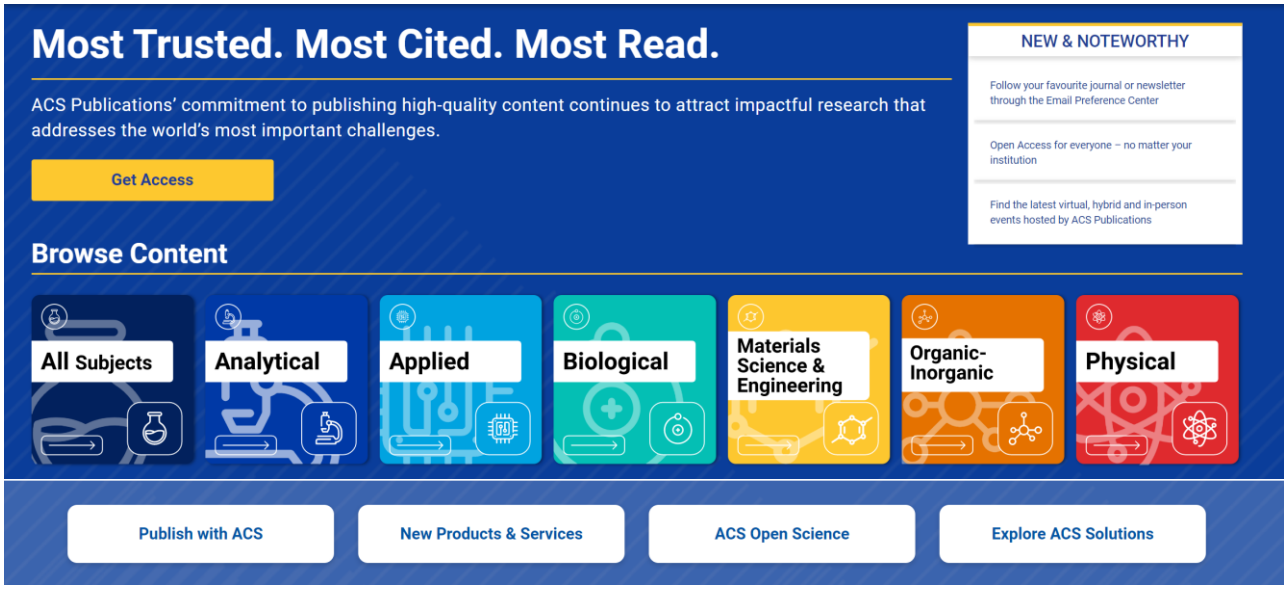

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Resources

- **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.

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

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

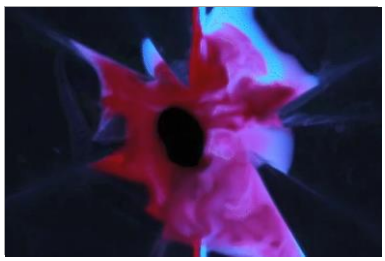
Microrobots que Limpian Agua Contaminada

Co-produced with the Sociedad Química de México

Thursday, November 2, 2023 | 2-3pm ET

Rebroadcast: 10 Tips for Creating Abstracts with Substance and Style

Previously co-produced with ACS on Campus



Thursday, November 16, 2023 | 2-3:30pm ET

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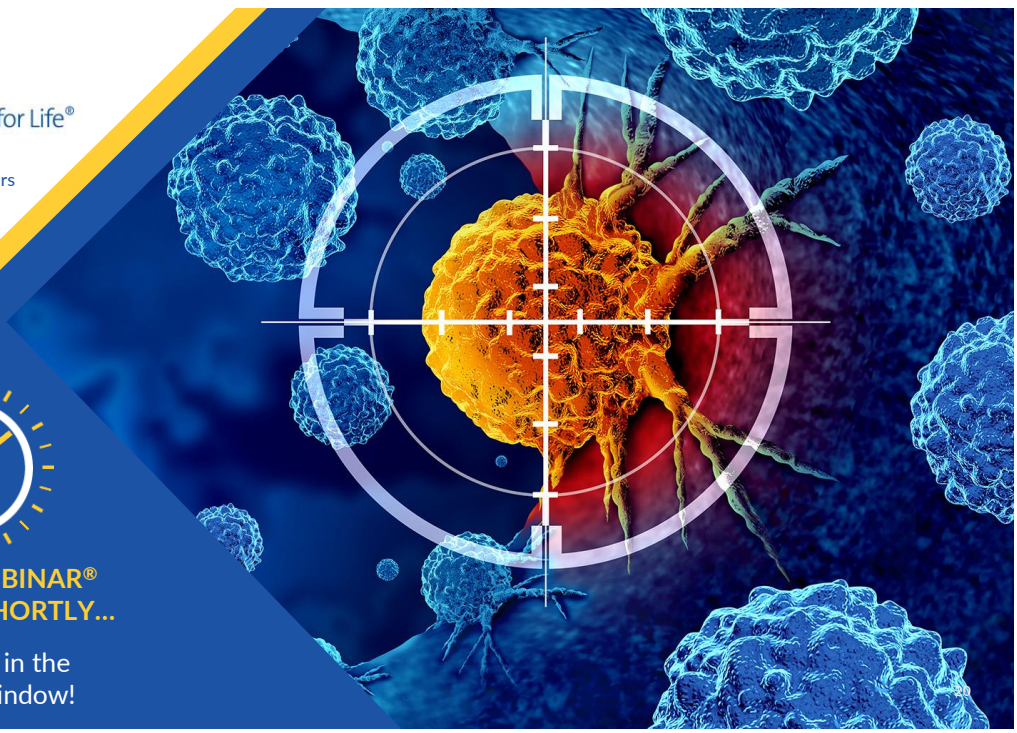

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A Bond Worth Forming: The Rise of Targeted Covalent Inhibitors

GARY GUSTAFSON, PHD

Senior Customer Success Specialist, CAS, a division of the American Chemical Society

NEIL DHAWAN, PHD

Co-founder and CEO, Totus Medicines

ANGELA ZHOU, PHD

Manager, Scientific Analysis and Insights, CAS, a division of the American Chemical Society

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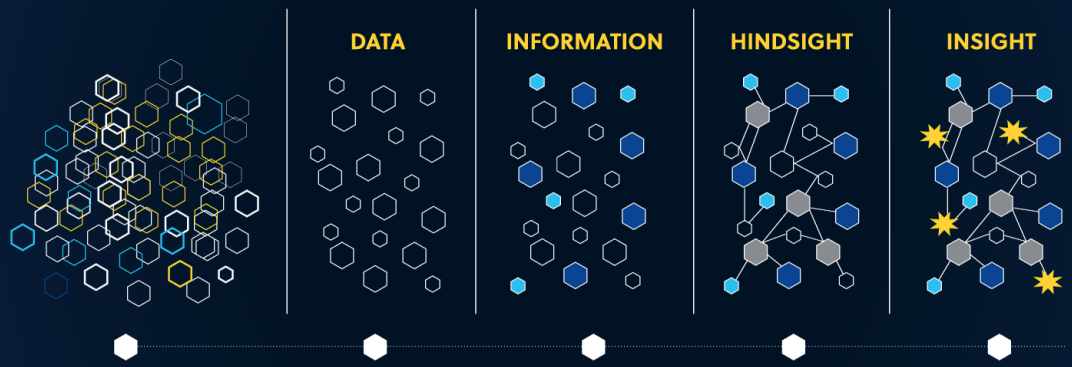
Data is valuable only when it is transformed into insight



CURATE to give data meaning

CONNECT information across disciplines

ANALYZE to reveal insights

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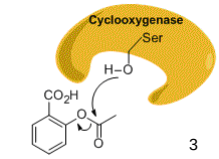
Covalent Inhibitors are not new

- Aspirin – NSAID (non-steroidal anti-inflammatory drug), COX inhibitor that decreases inflammation through the suppression of prostaglandin and thromboxane synthesis (requires COX enzyme)
- Used as a therapeutic for 125 years, 17M prescriptions in 2020 [1]
- Off-target: Stomach ulcers, worsening asthma, among others[2]



3

Acetyl salicylic acid

1) *"Aspirin - Drug Usage Statistics, US 2013-2020"* ClinCalc
2) American Society of Health-System Pharmacists. 29 November 2021
3) doi:10.1515/9783110468755-002

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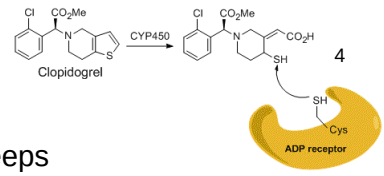
Covalent Inhibitors are not new



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- Clopidogrel (Plavix) – alkylates receptor on platelets that keeps them from sticking together and forming clots.
- Before expiration of its patent in 2011 it was the #2 selling drug in the world[1]
- Compound is a prodrug, so less side effects but there are incidences of thrombotic thrombocytopenia purpura[2] and hemorrhage[3]
- With both drugs, covalency was not planned but serendipitous

1) doi:10.1038/nm0111-40
2) doi:10.1161/01.STR.0000109253.66918.5E
3) doi:10.1016/S0140-6736(04)16721-4
4) doi:10.1515/9783110468755-002

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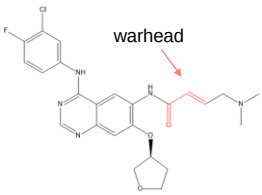
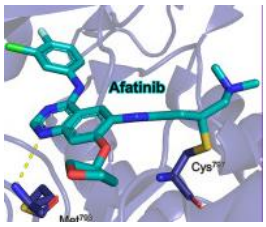
Rise of Targeted Covalent Inhibitors (TCI)



Afatinib

- Toxic side effects arising from non-selective reactivity led many companies to shy away from covalent inhibitors in early 2000s
- Researchers tried incorporating electrophiles (warheads) that would only react when in position at site of action
- Afatinib, the first approved drug using TCI approach[2], bound to EGFR receptor putting α,β-unsaturated ketone in position to form covalent bond with Cys^{797}



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1) doi: 10.1158/1535-7163.mct-17-0324
2) doi: 10.1007/s40265-013-0111-6

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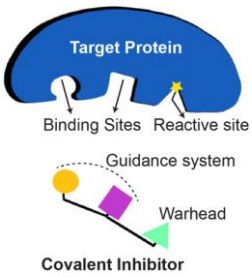
Theory of Targeted Covalent Inhibitors (TCI)

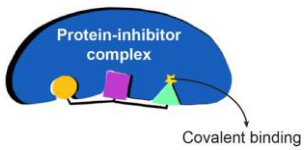
Leverages a guidance system and warhead

1. Guidance system brings molecule to site of interest



2. Aligns warhead to react with residue

3. Covalent bond is formed with the target



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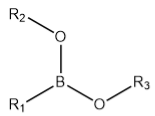
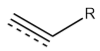
Other Warheads Used in TCIs

– Although α,β-unsaturated ketone functionality has been the most common warhead, many others have been incorporated as well.



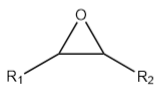
Boronic Acid/Ester

Aldehyde

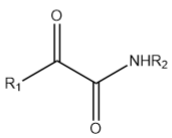


R = -CN, -CO
-NO2, -SO2

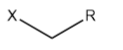
Alkenes, alkynes w/ EWG



Epoxide



α-ketoamide



R = -CN, -CO
-NO2, -SO2

Halogens w/ EWG

30

Advantages of TCIs (Over Non-covalent Inhibitors)

- Due to high biochemical efficiency, TCIs may require less compound and have fewer off-target effects[1]
- Prolonged binding can result in less-frequent drug dosing[2]
- Forming covalent bonds may help overcome endogenous substrates[3]
- If strength of binding does not need to be as high, “undruggable” enzymes with shallow or non-discrete binding sites, like those involved in protein-protein interactions, can be targeted[4]

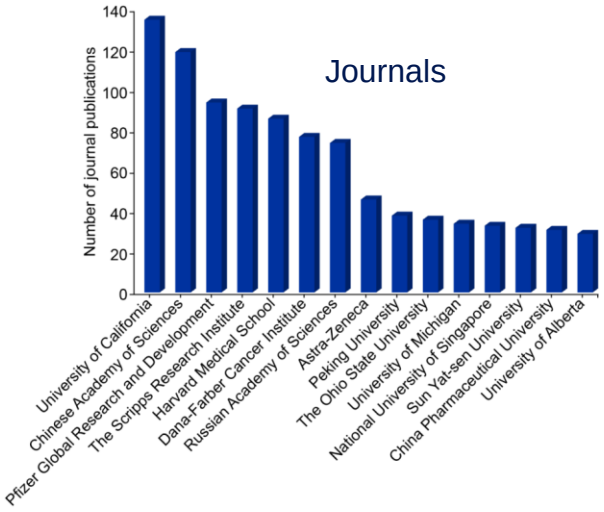
1) DOI: 10.1038/nrd1500
2) DOI: 10.1016/s0149-2918(01)80109-0
3) DOI: 10.1021/jm3003203
4) DOI: 10.1021/acs.jmedchem.9b00561

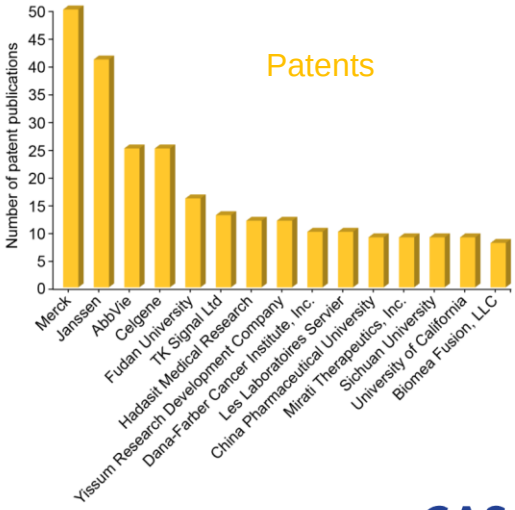
Literature Trends in TCI Publications

- With the tremendous rise in the research being done on targeted covalent inhibitors, an exercise was undertaken to look at the trends in the publications and the compounds themselves.
- To do this, searches were executed using the CAS Content Collection™.
- Year of publication and publishing institution were captured to look for any trends as well as warheads, targets and therapeutics areas.

Total Publications: Journals vs. Patents

2000-2022





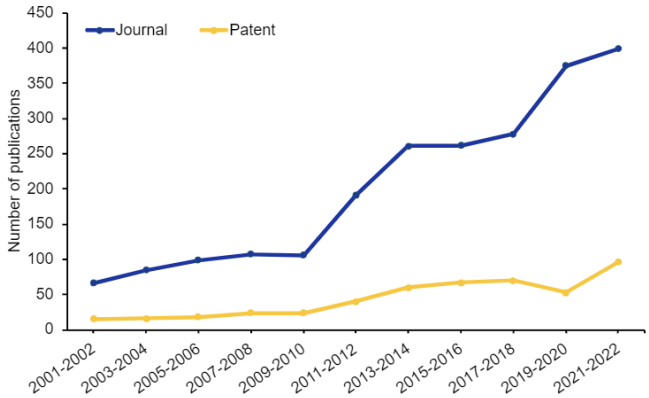
Total Publications and Patents Accelerating

Across the CAS Content Collection: Includes all warheads

- Year of publication and publishing institution were captured to look for any trends as well as warheads, targets and therapeutics areas.

Key inflection points:

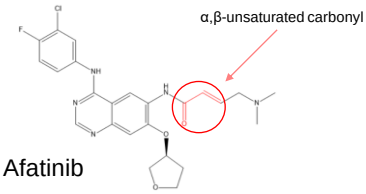
- 2011-12: possibly due to several TCIs in clinic approaching first approvals
- 2019-20: Publications in journals up/patents down, Possibly due to Covid lock down?



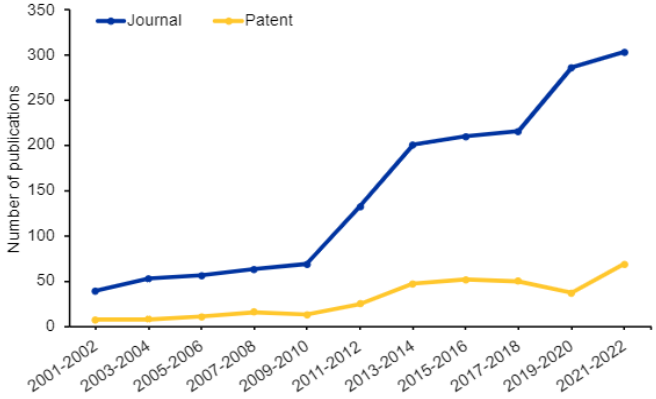
Total Publications: α,β-unsaturated Carbonyls

Trend looks similar as total publications

- α,β-unsaturated carbonyls dominate publications
- Inflection 2011-12: Several α,β-unsaturated carbonyls in clinic (Afatinib and Ibrutinib among others)

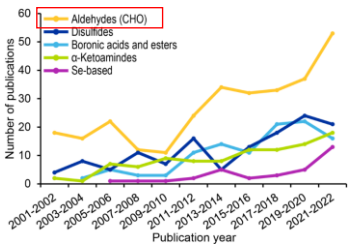


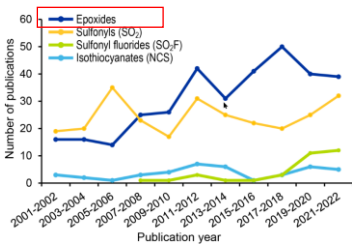
Afatinib

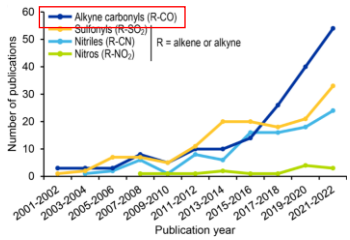


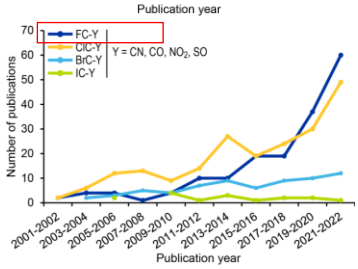
Warheads Publication by Year

Significantly fewer publications than α,β-unsaturated carbonyls



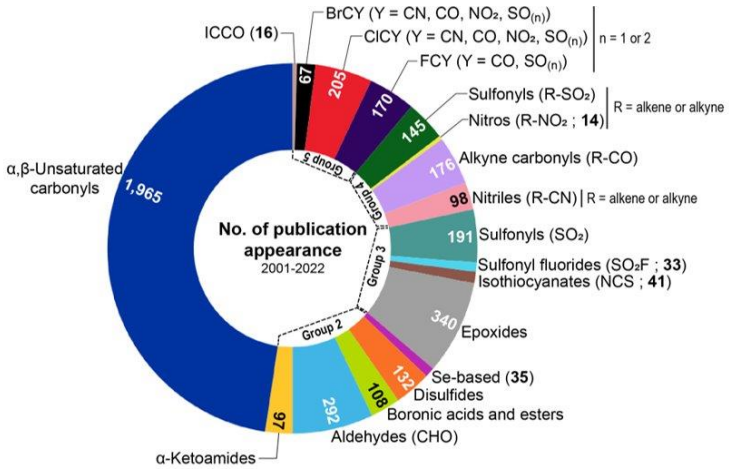


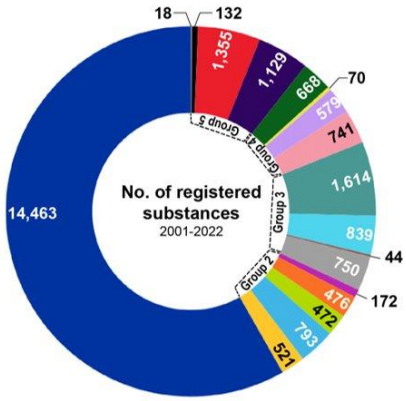




Warheads by publication and CAS RN™

α,β-unsaturated carbonyls dominate publications and substance count





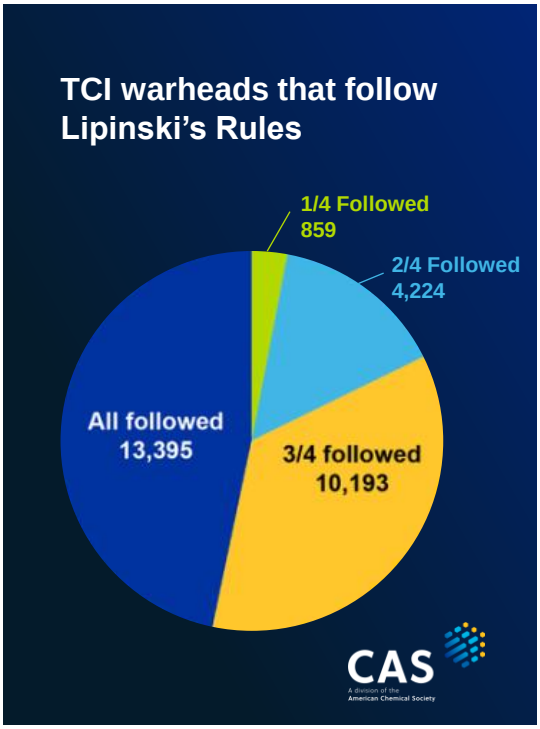
37

Landscape of TCI Warheads

Through Lipinski's rules

Overall, TCIs are compliant with Lipinski rules:

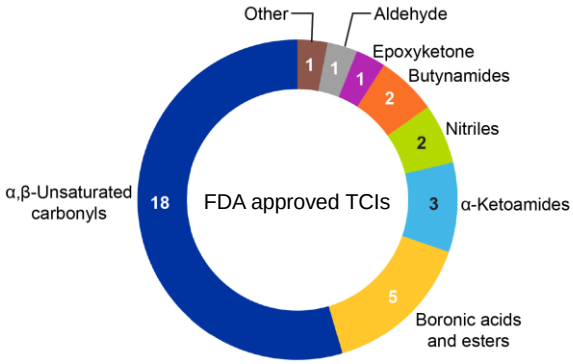
- 82% follow 3 or all 4 rules
- Perhaps due to overall lower average MW due to less rigorous binding affinity requirements?

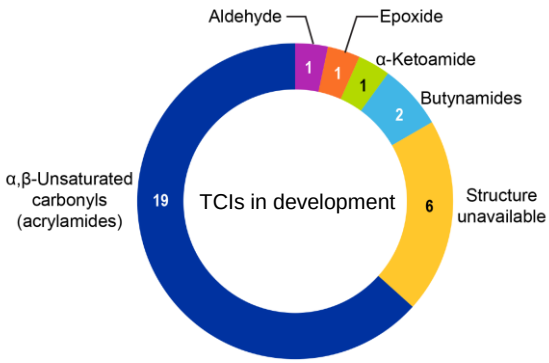


38

Comparing Approved TCIs with Those in Clinic

Warhead distribution

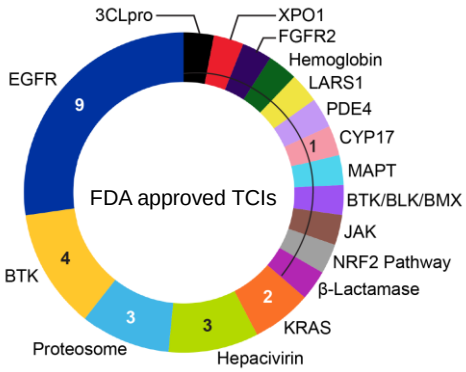


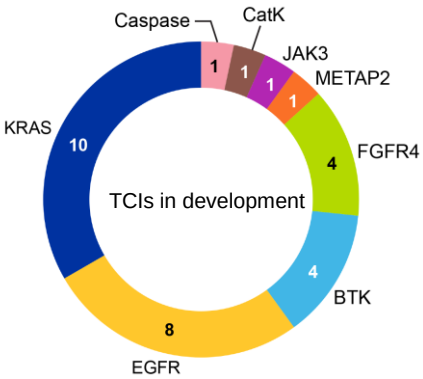


Similar warhead distribution

Comparing Approved TCIs with Those in Clinic

Protein target distribution



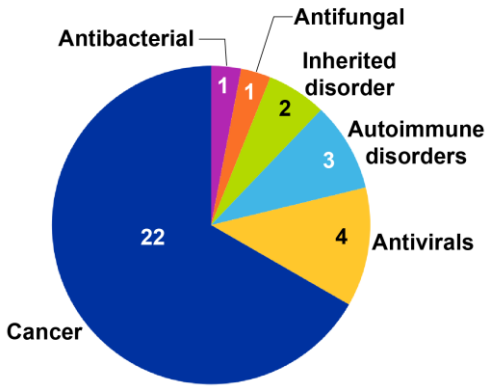


KRAS emerging as potential target;

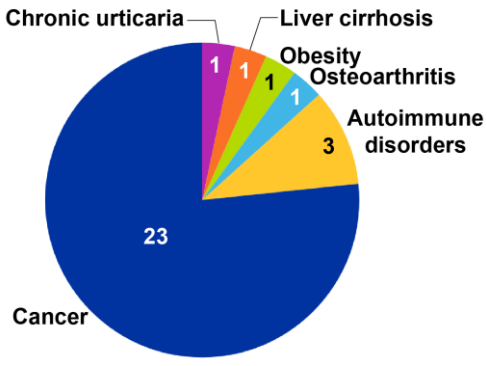
EGFR and BTK continue to be targeted

Comparing Approved TCIs with Those in Clinic

Disease/Indication distribution



FDA approved TCIs

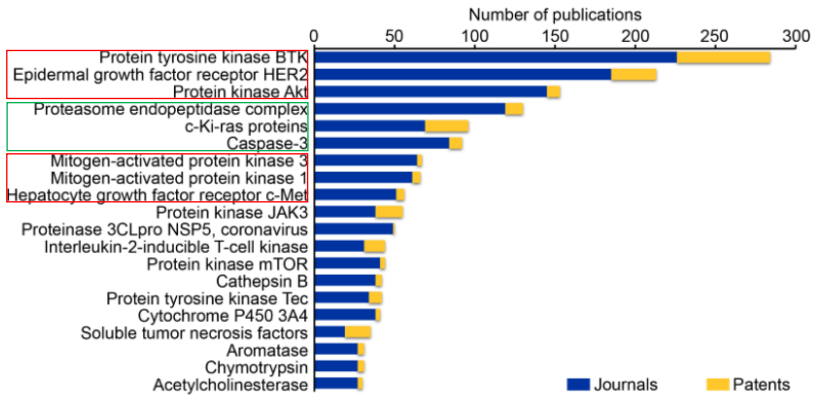


TCIs in development

Most TCIs in development continue to be for cancer therapy

Most Common Targets of TCIs and Cancer Links

- By searching the CAS Content Collection™, the top 20 targets associated with targeted covalent inhibitors by number of publications were identified.
- Kinases often activated in human cancer
- Have been investigated for cancer therapy



Summary of Trends in Publications on TCIs

- Research in TCIs (evidenced by publications and approved drugs) has shown consistent growth over the last 20+ years
- The ability to target covalent bond formation has benefits in efficiency, specificity and fewer side effects compared to non-covalent inhibitors
- α,β-unsaturated carbonyls are the most frequent warhead used but a variety of warheads are being employed
- 82% of published TCIs have 0 or 1 Lipinski violation
- In a sampling of TCIs in the clinic or approved drugs, 73% are cancer therapies
- EGFR and BTK are the most common targets of approved TCIs but KRAS dominates among TCIs in clinic and many other targets found in literature

CAS
A division of the American Chemical Society

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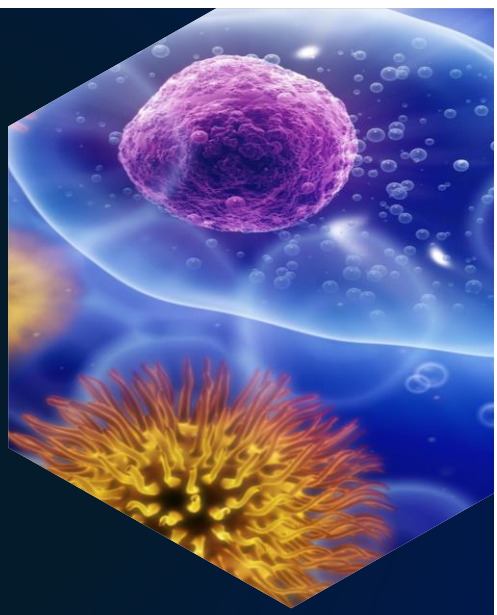
Gain insights on the landscape of covalent inhibitors and more

Unique analysis of a wide range of topics
cas.org/insights



- Articles
- Executive Summaries
- Insight Reports
- Journal Publications

Gary Gustafson, PhD
Senior Customer Success Specialist
ggustafson@cas.org

CAS
A division of the American Chemical Society

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Totus Medicines

Creating new, lifechanging therapeutics repeatedly through revolutionary innovations in chemistry, biology, and AI

October 2023

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Power: Covalency is Key

Undruggable targets require special tools to create drugs that bind

11

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Power: Covalency is Key

Covalent Drugs Form a Precise Covalent Bond with the Drug Target

Covalent drugs represent some the most impactful drugs of all time:

- Penicillin
- AZT
- Statins
- Cancer Alkylating Agents

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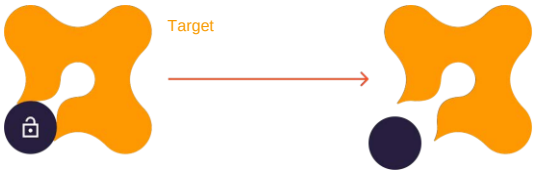

Typical ionic drugs bind weakly and fall off which leads to less effective drugs

Covalent Modifier

Covalent drugs create a foothold and bond to the target which leads to extremely effective drugs

Power: Covalency is Key

Covalent Properties Enable Remarkable Developmental Advantages

	Covalent drugs	Ionic drugs
Percent approved after Phase II (modern covalents)	20%	1%
Time from IND to approval (modern covalents)	6y	10y
Percent safe & essential medicines (WHO list)	25%	2%

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8

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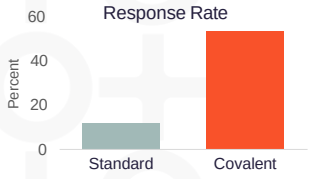
Power: Covalency is Key

Covalency Can Solve Multi-billion Dollar Healthcare Problems

Kras-G12C Lung Cancer

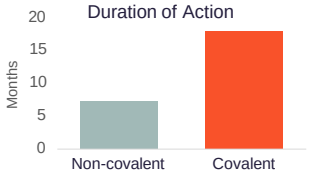
100,000 New cases per year



Undruggable Target

EGFR-mutant Cancer

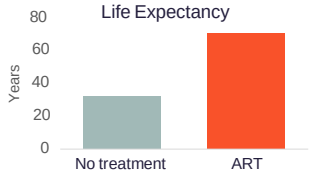
200,000 New cases per year



Resistant Target

HIV / AIDS

1,300,000 New cases per year



Non-protein Target (DNA/RNA)

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Power: Covalency is Key

So Why Are Less Than 2% Of Drugs Covalent?

01

Prevailing perception that specificity is too difficult to achieve, raising safety concerns

02

Lack of high-throughput screening technology for covalent drugs resulting in lengthy, costly discovery timelines

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Power: Covalency is Key

Covalent Drug Perceptions and Reality Dramatically Diverge

Covalent drugs are as safe, and sometimes safer, than non-covalents

Grade ¾ toxicities	Non-covalent	Covalent
EGFR	25%	5%
BTK	6%	4%
Proteasome	7%	7%

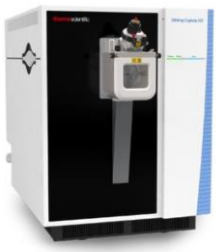
Covalents have led to repeated blockbusters and >$10B acquisitions

BUSINESS
AbbVie to Buy Pharmacyclics in $21 Billion Deal

BUSINESS
Amgen Strikes $10.4 Billion Deal for Onyx

PHARMA
Forget Tagrisso's $3B sales target. It'll be double that by 2013, analyst says

We now have the technologies to evaluate the safety of covalent drugs



Mass Spectrometry

5
1

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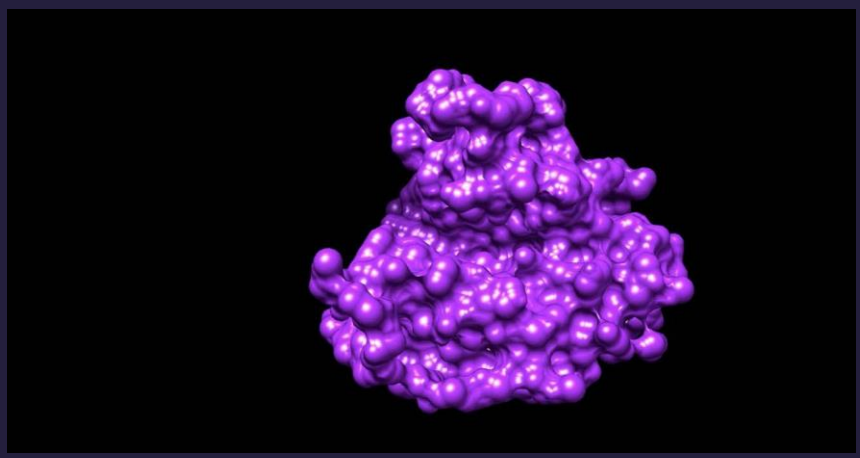
Power: Covalency is Key

Conventional Design of Precise Covalent Drugs is Challenging

Researchers must find a needle in a haystack.

Effective identification of a precise covalent drug results in profound pharmaceutical advantages including:

- Very High Potency
- Binary Specificity
- PK/PD Independence
- Built-in Biomarker



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A great example

Following the path of a proven, covalent drug in resistant lung cancer

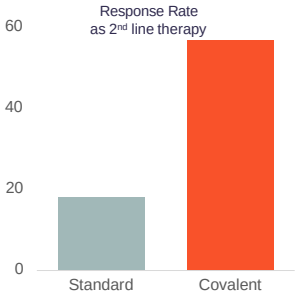
Cancer develops resistance to typical drug

TAGRISSO® osimertinib

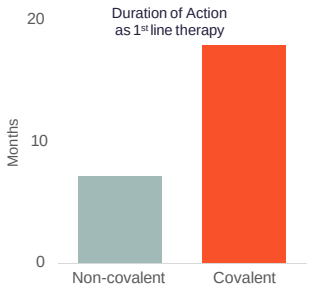
EGFR-mutant Lung Cancer

$6 Billion Annual Market as first-line therapy

Covalent drug is effective against resistance



Covalent outperformed the non-covalent drug



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+O+US

TOS-358 - The first clinical-stage covalent inhibitor of PI3Kα

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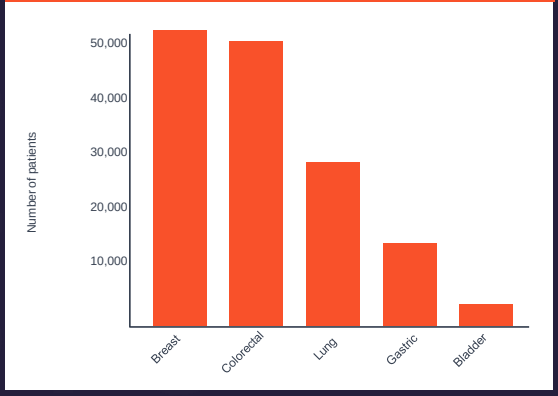
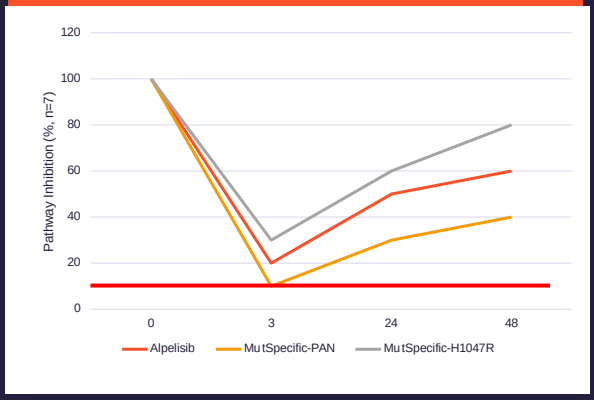
PI3Kα is one of the most significant unmet needs in oncology

PI3Kα is one of the most mutated cancer oncogene (~15% of all cancers)



Current molecules do not durably inhibit the pathway and have proven ineffective in the clinic



55

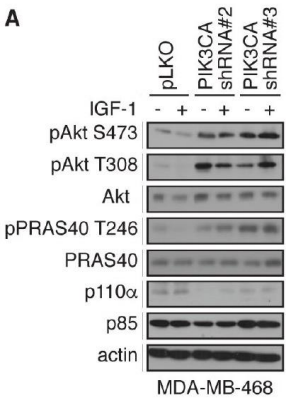
CRISPR deletion and full knockout (equivalent to 100% inhibition) induces cell death in PI3K-alpha mutant cells across different tumor types

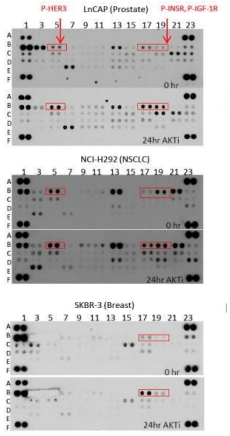
	Bladder	Colon	Lung	Gastric	Breast	NSCLC	Mela-noma	NSCLC	All	All	All	All
Mutated Gene	PIK3CA	PIK3CA	PIK3CA	PIK3CA	PIK3CA	EGFR	BRAF	KRAS	All	All	All	All
CRISPR Knockout Gene	PIK3CA	PIK3CA	PIK3CA	PIK3CA	PIK3CA	EGFR	BRAF	KRAS	PIK3CA	EGFR	KRAS	BRAF
Average Gene Effect	-1.03	-0.95	-0.86	-0.99	-1.02	-0.61	-0.91	-1.12	-0.36	-0.26	-0.39	-0.07

*Data has been updated with most recent version
https://depmap.org/portal/

56

Knockdown of PIK3CA leads to robust pathway re-activation



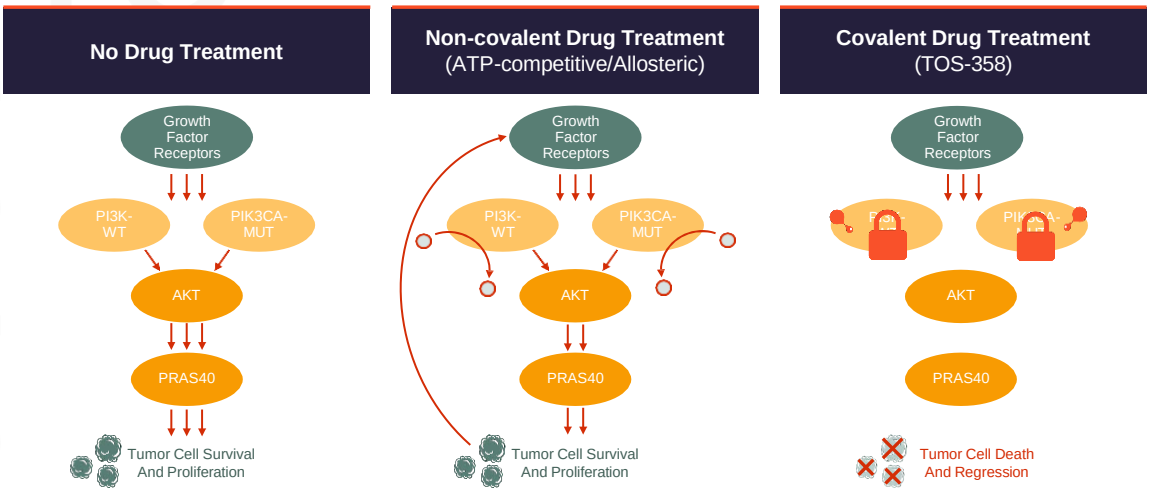


Robust RTK activation occurs across cell lines in response to PI3K-AKT inhibition

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3025058/

57

Totus' goal was to develop a molecule that can achieve complete inhibition of PI3Kα in a highly specific manner



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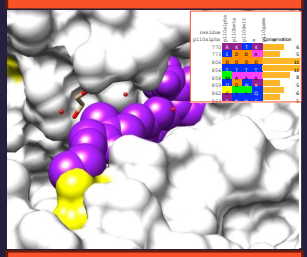
Totus platform delivered the first highly specific covalent inhibitor against PI3Kα, which is mutated in ~15% of all cancers

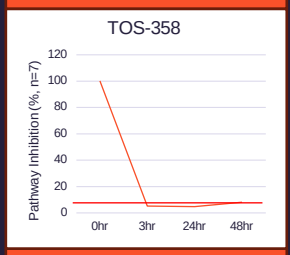
TOS-358- 4 months to discovery, 24 months to the clinic

First, Specific Covalent Inhibitor



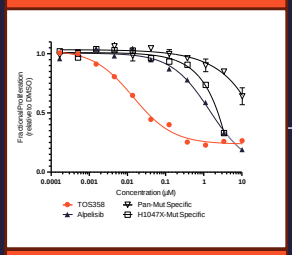
Targeting a unique cysteine in PI3K-alpha

Feedback inhibition



Sustained pathway inhibition across PI3Kα-mutant cell lines

Superior Efficacy



No sustained hyperglycemia and no DLTs at maximal efficacious doses

TOS-358 FIH 1st Q'23

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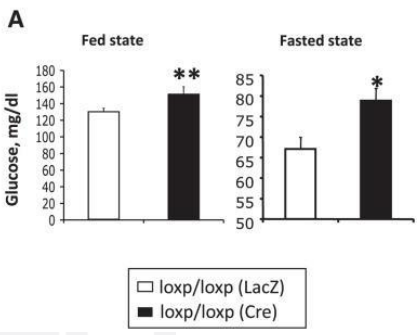
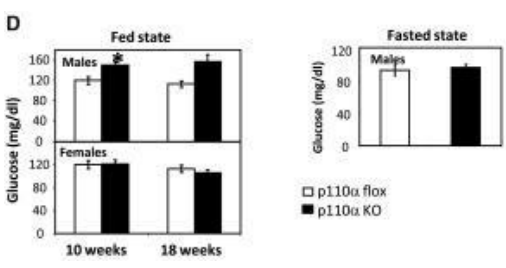
PI3K-alpha knockouts can induce limited glucose increases, but no sustained hyperglycemia

Acute Effects



Chronic Effects



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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3144706/

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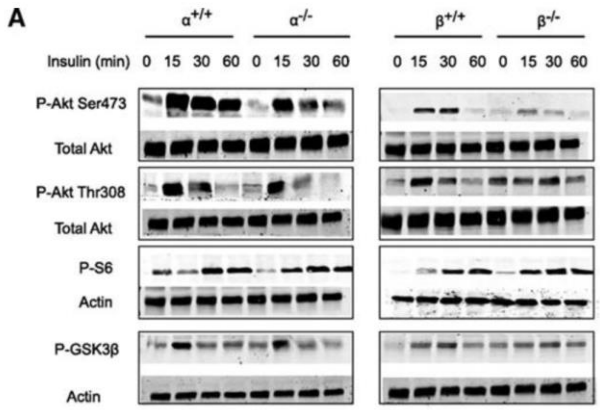
PI3K-alpha knockout in liver does not induce sustained hyperglycemia



	p110-α+/+	p110-α-	p110-β+/+	p110-β-
Glucose (mg/dL)	119 ± 2	118 ± 1	109 ± 4	150 ± 4*

17

https://diabetesjournals.org/diabetes/article/60/5/1483/33574/Ablation-of-PI3K-p110-Prevents-High-Fat-Diet

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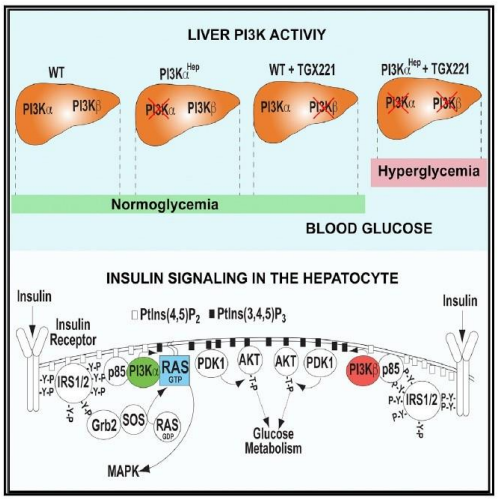
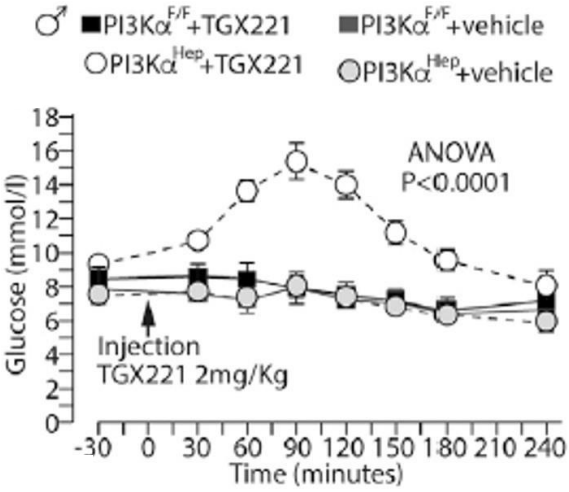
PI3K-alpha liver knockout does not induce sustained hyperglycemia

Graphical Abstract





62

https://pubmed.ncbi.nlm.nih.gov/30982732/

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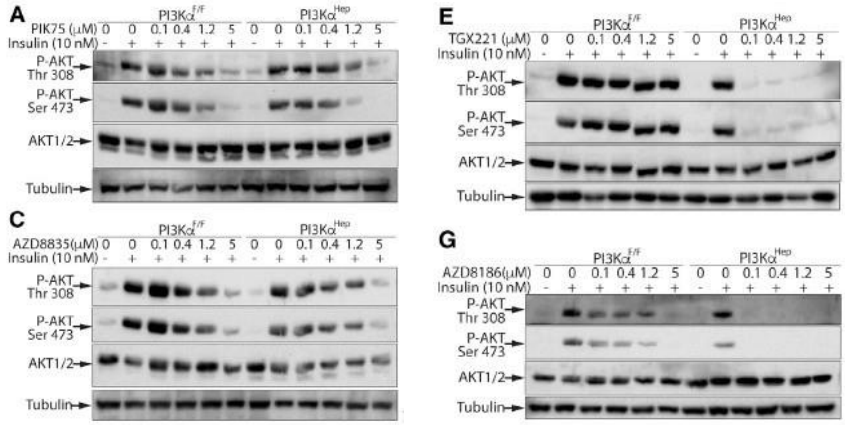
“Alpha-selective” inhibitors block PI3K signaling in the absence of PI3K-alpha

Name	IC_{50} p110α	IC_{50} p110β	IC_{50} p110γ	IC_{50} p110δ
PIK75	**5.8 nM**	1.3 μM	76 nM	510 nM
AZD8835	**6 nM**	431 nM	90 nM	6 nM
TGX221	5 μM	**5 nM**	>10 μM	100 nM
AZD8186	35 nM	**4 nM**	675 nM	12 nM

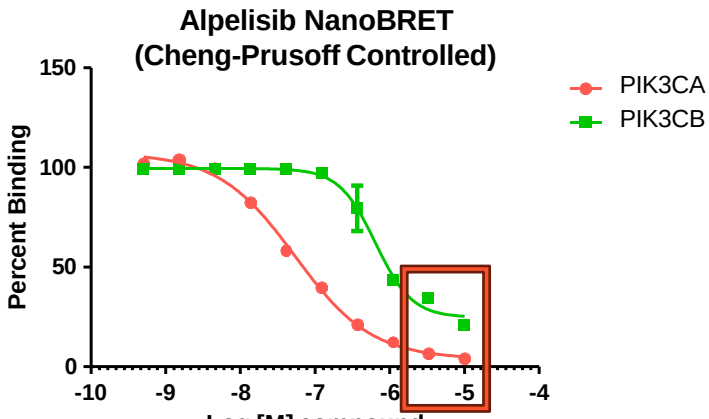


63

https://pubmed.ncbi.nlm.nih.gov/30982732/

63

Alpelisib achieves a poor cellular window of PI3Ka/PI3Kb inhibition



	PIK3CA	PIK3CB
IC50	5.397e-008	6.441e-007

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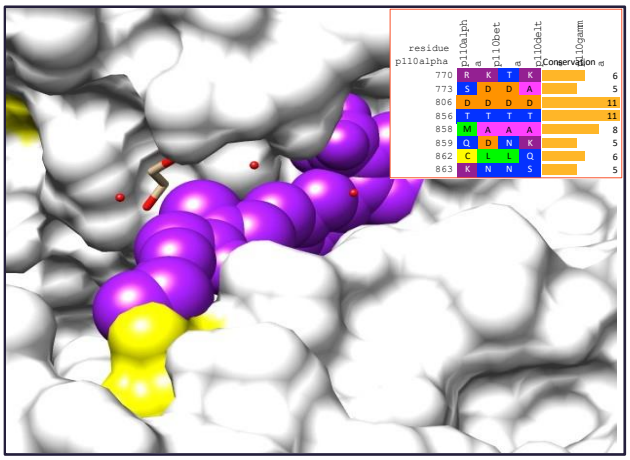
TOS-358 bonds a unique cysteine in PI3K-alpha



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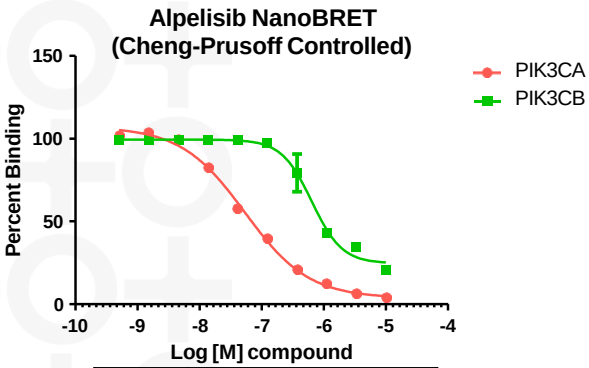
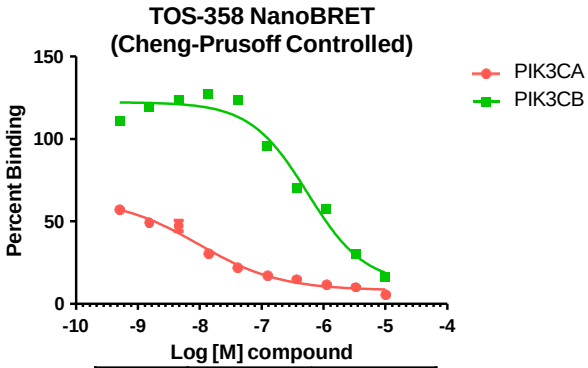
TOS-358 achieves a significant cellular window of PI3Ka/PI3Kb inhibition



	PIK3CA	PIK3CB
IC50	5.397e-008	6.441e-007

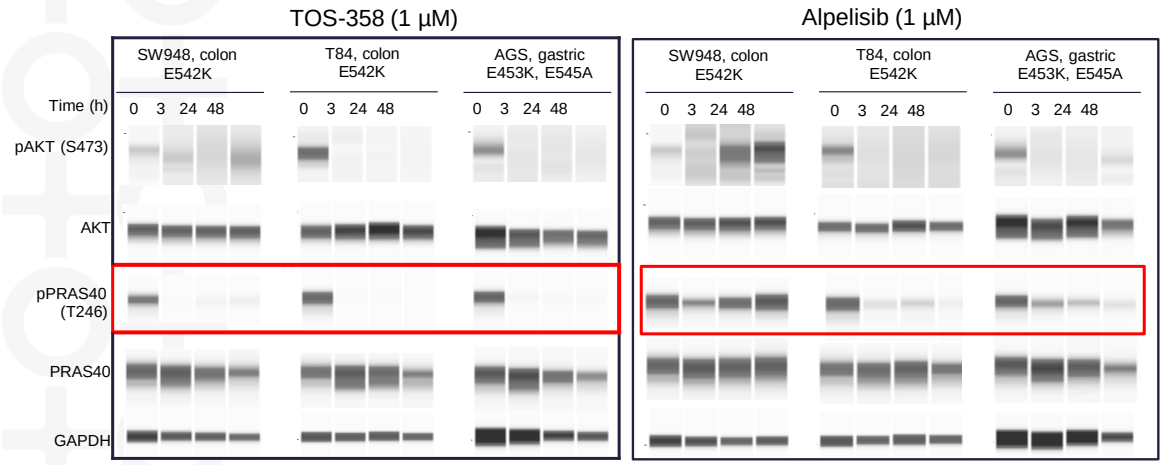


	PIK3CA	PIK3CB
IC50	9.584e-009	5.578e-007

66

66

TOS-358 achieves near complete inhibition of downstream signaling



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https://pubmed.ncbi.nlm.nih.gov/30982732/

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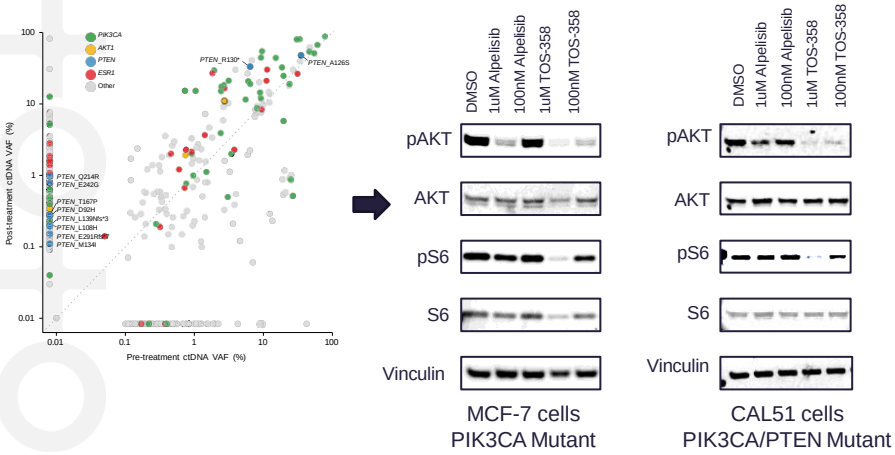
TOS-358 can also inhibit signaling in Alpelisib-resistant settings



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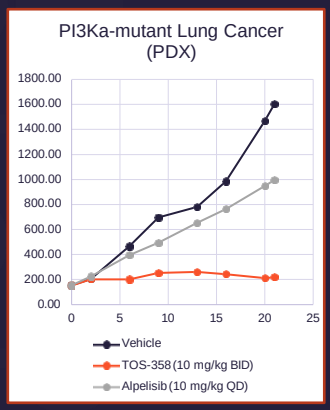
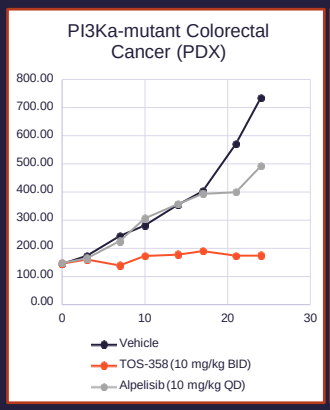
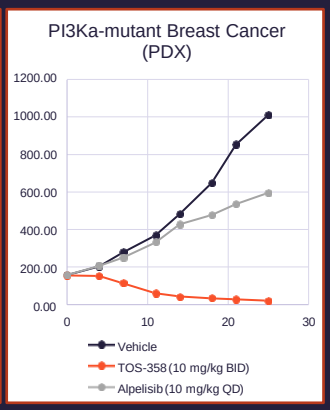
TOS-358 can uniquely shut down PI3Kα leading to superior efficacy across multiple tumor subtypes (Mouse T1/2= ~2 hours)







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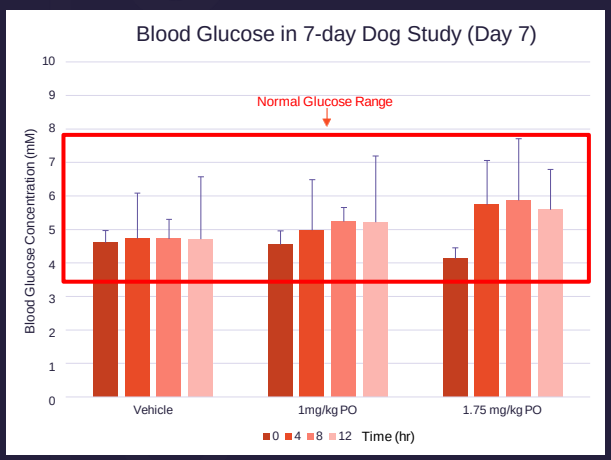
TOS-358 can max out target engagement with no DLTs in preclinical models



Therapeutic Window in 28-day GLP Studies			
	TOS-358	Alpelisib	Copanlisib
Rat	>100X	0.3X	0.2X
Dog	>10X	0.2X	0.6X

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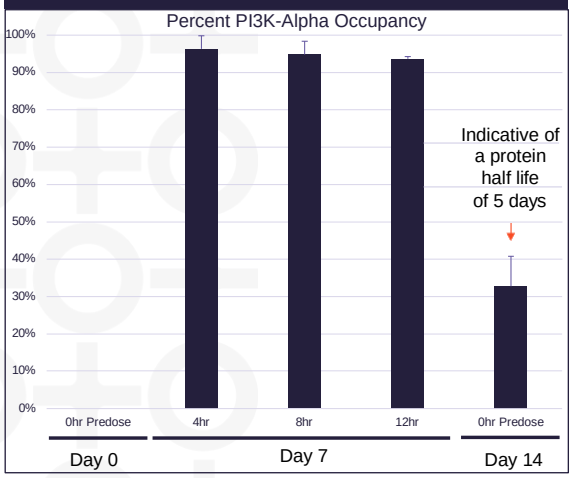
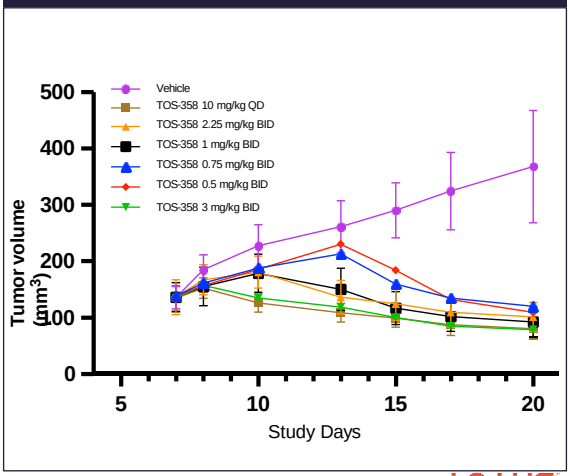
TOS-358 demonstrates profound and continuous inhibition at low doses through accumulation on slow turnover PI3Ka (dog, mouse)

Dog study with 7-day treatment with 1 mg/kg QD with 7 day drug washout reveals >5 day PI3Ka protein half life



Low dose treatment (0.5mg/kg) can accumulate on target to induce stable regressions after 6-7 days



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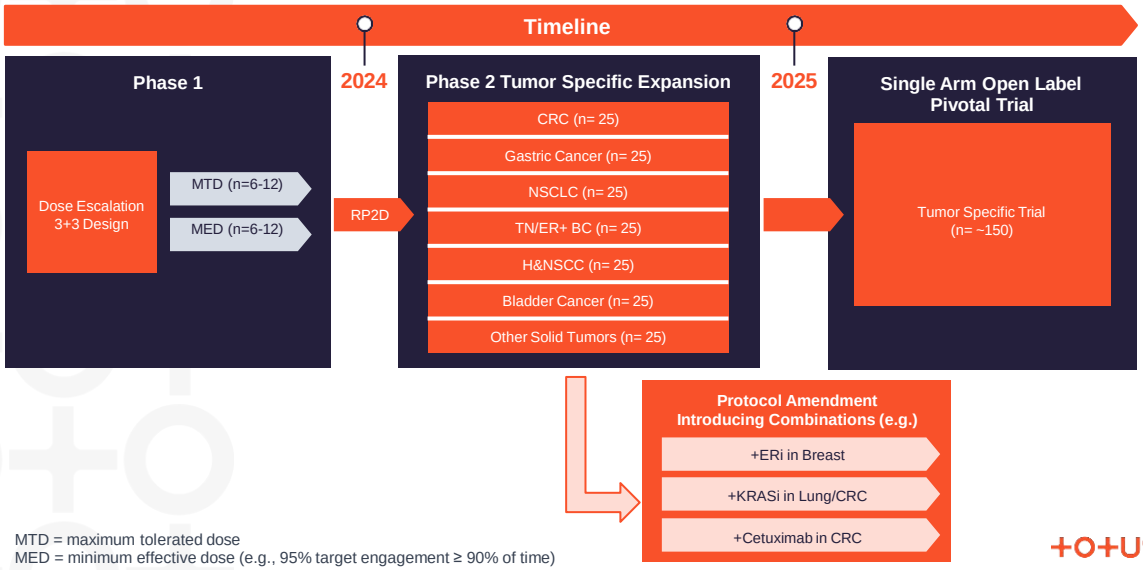
Totus has established a seamless clinical approach across multiple PI3K*a* mutant tumors to support an accelerated approval path



MTD = maximum tolerated dose
MED = minimum effective dose (e.g., 95% target engagement ≥ 90% of time)

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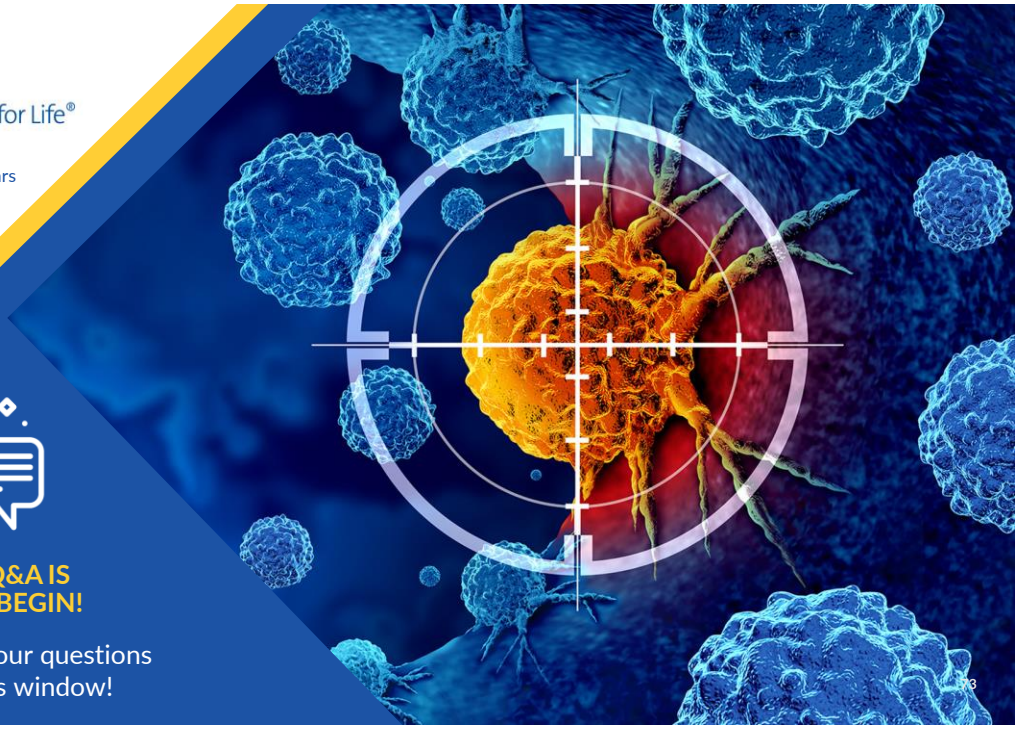

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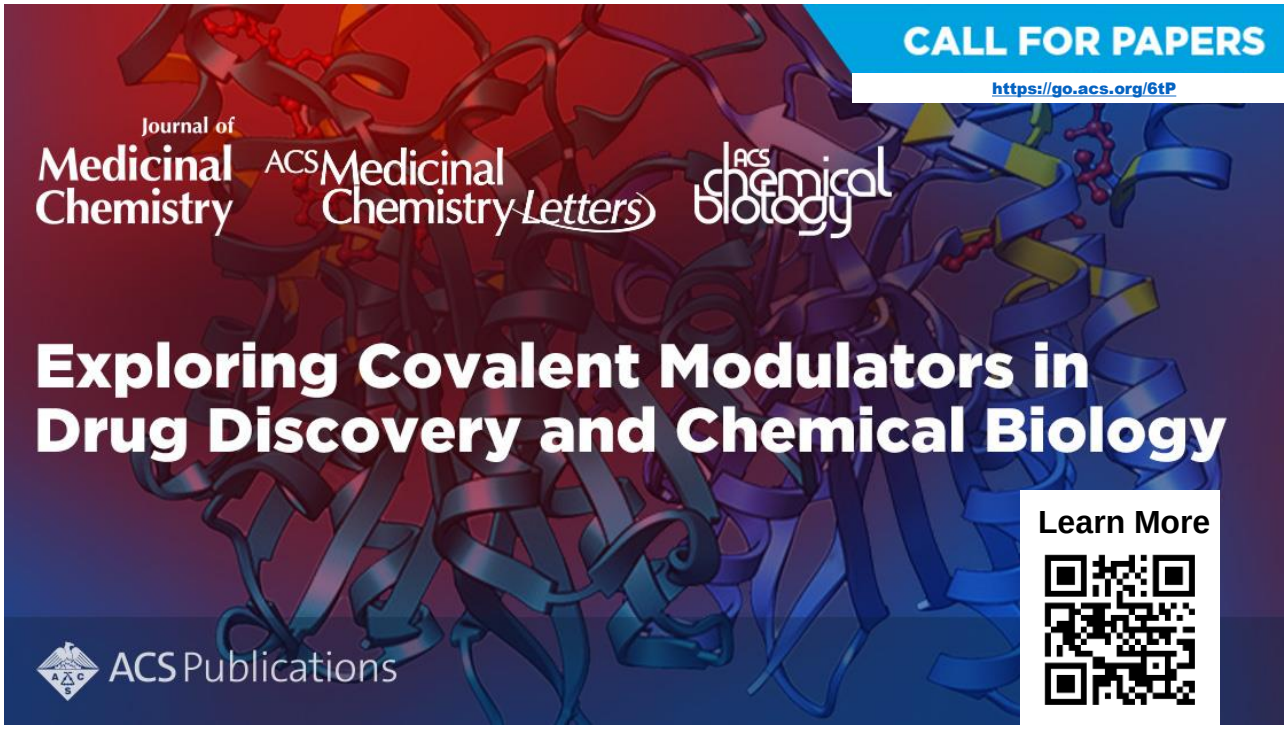
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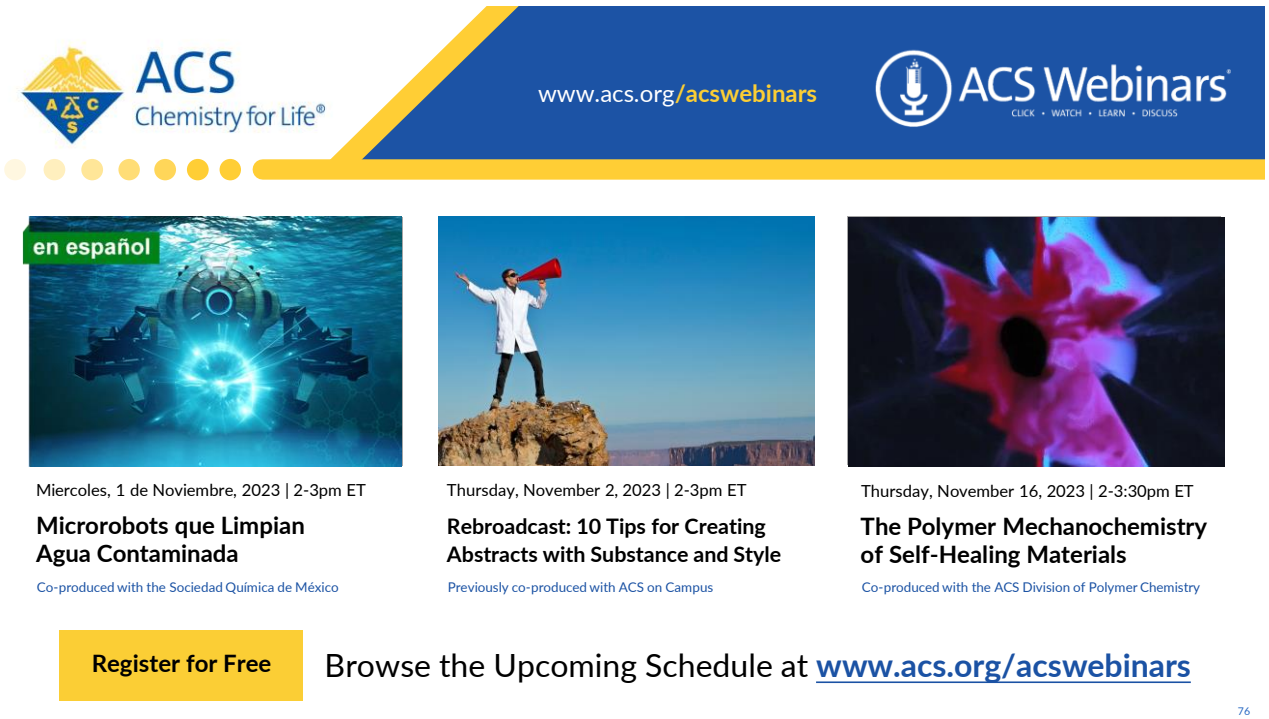
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