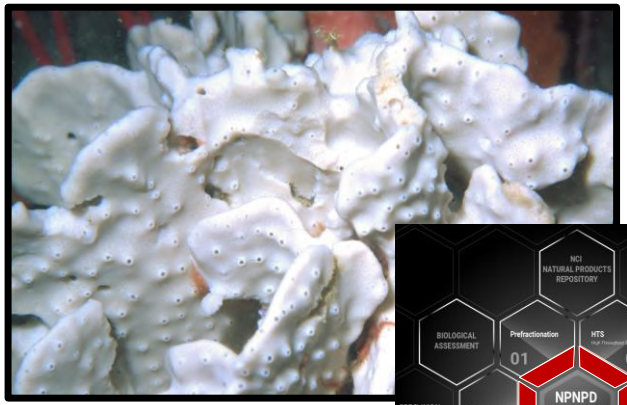
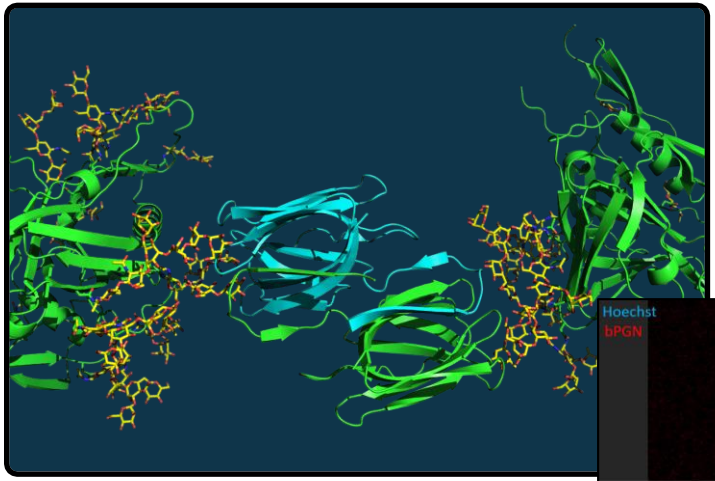
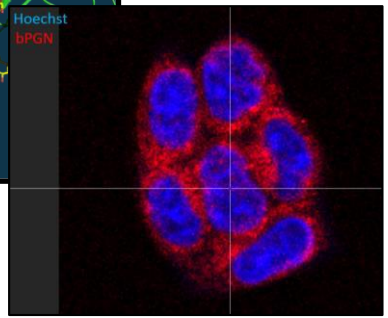
Natural Product Discovery in the 21st Century





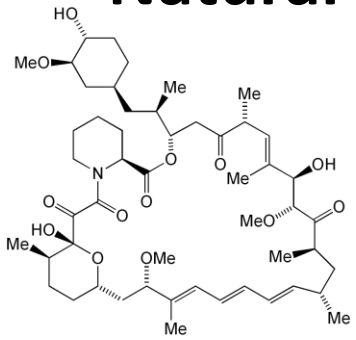


Barry R. O'Keefe

Director, Molecular Targets Program, Center For Cancer Research, and Chief, Natural Products Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, NIH, USA

FAPESP School 60th Anniversary, August 9, 2022

Natural Products: A History of Pharmaceutical Utility



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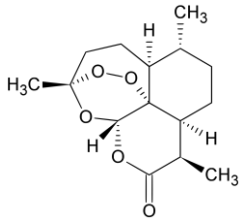

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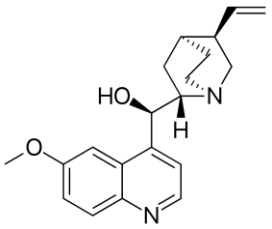

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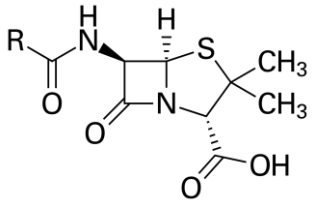

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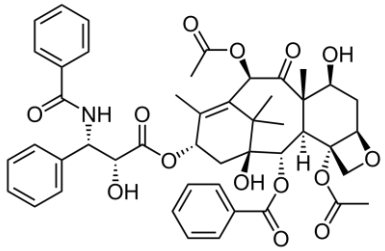

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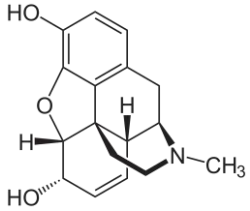
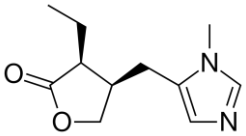
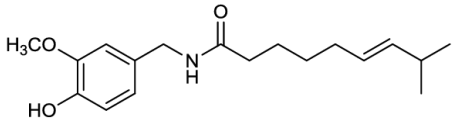


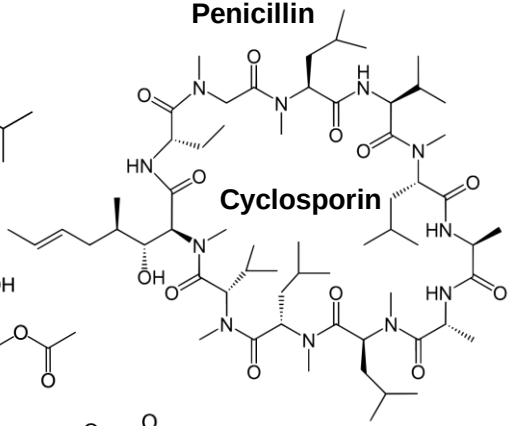
Morphine



Pilocarpine



Capsaicin



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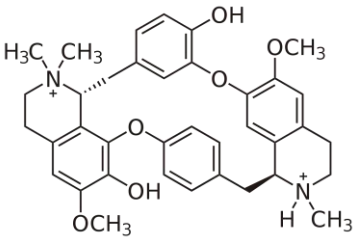
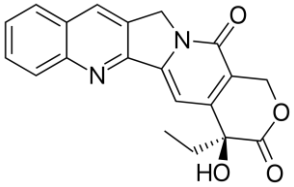
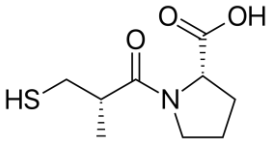


Tubocurarine

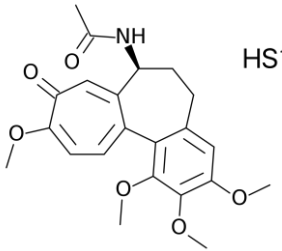


Camptothecin

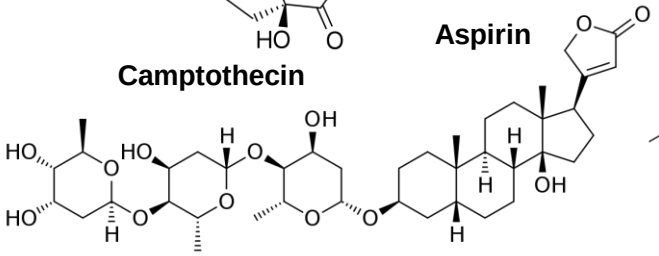
Aspirin



Captopril



Colchicine



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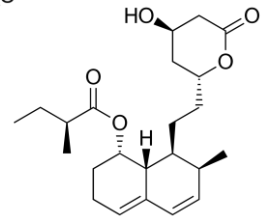
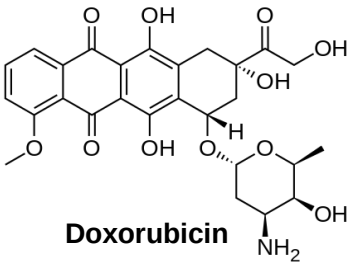


Mevastatin



Doxorubicin

Natural Products: A History of Pharmaceutical Utility



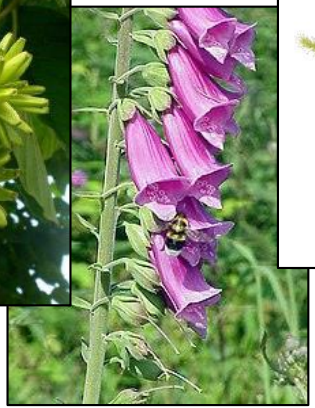
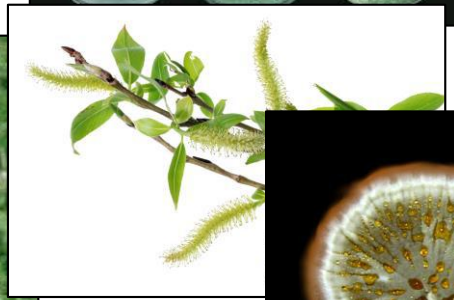
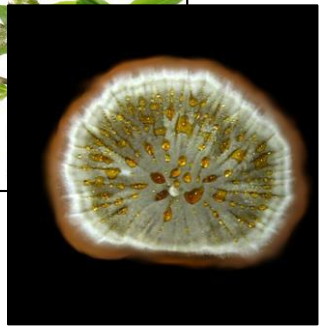
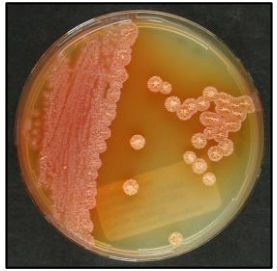




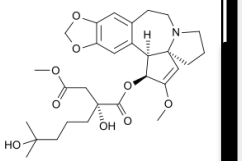




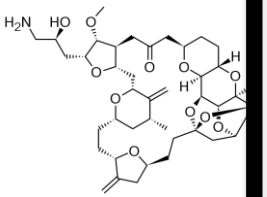


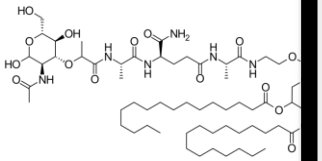
Natural Products and Drug Discovery and Development



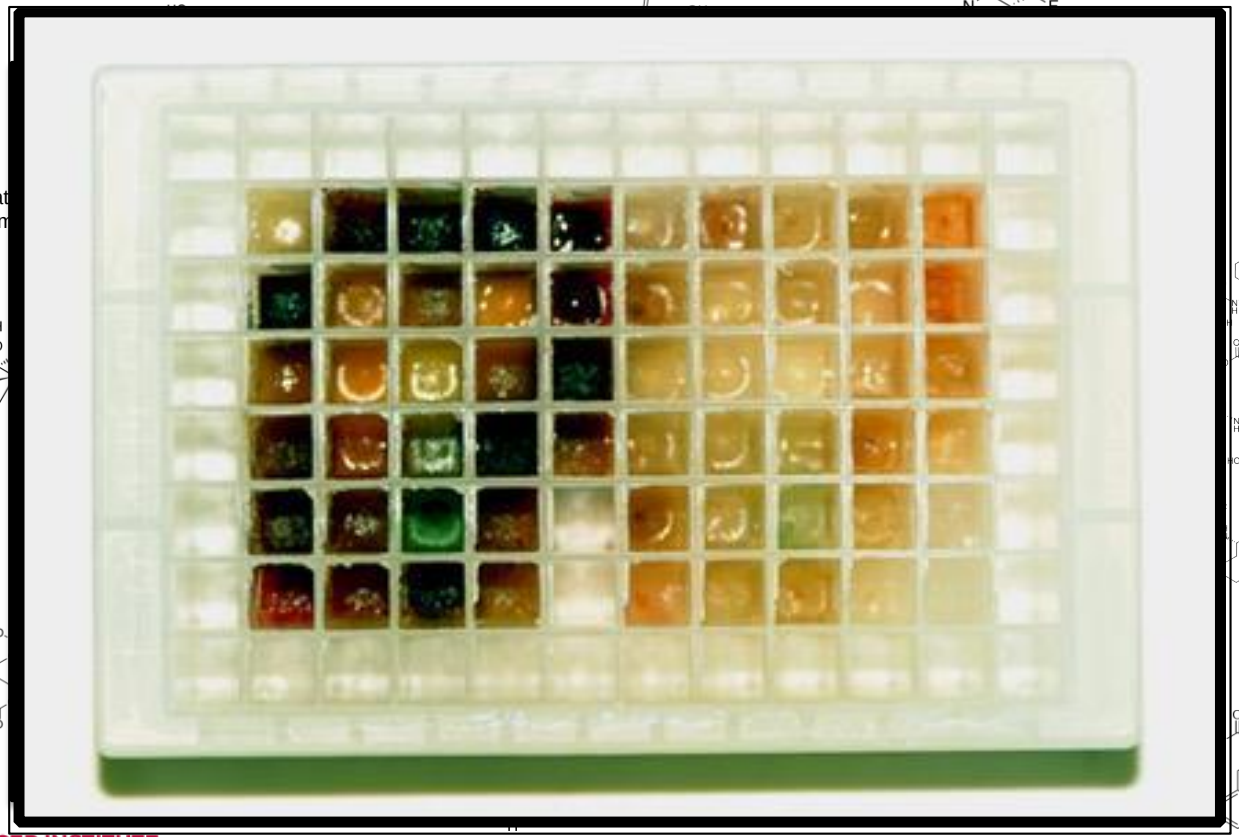
Omacetaxine mepesuccinat
Chronic myelogenous leukem

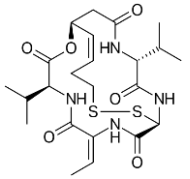


Eribulin
Metastatic breast cancer

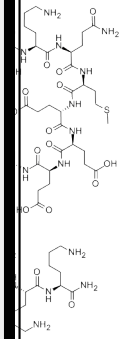


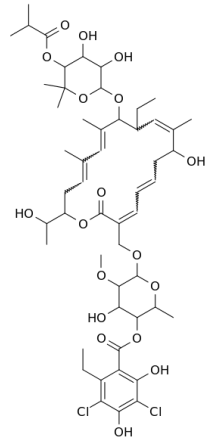
Mifamurtide
Osteosarcoma



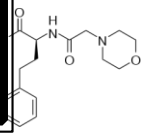


Romidepsin
T-cell Lymphomas





Fidaxomicin
Antibiotic

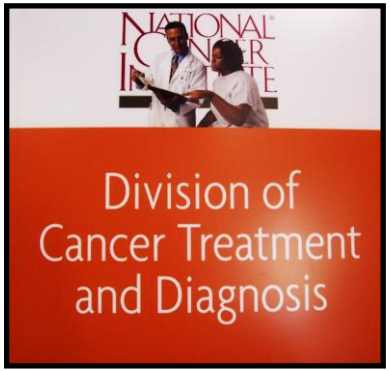


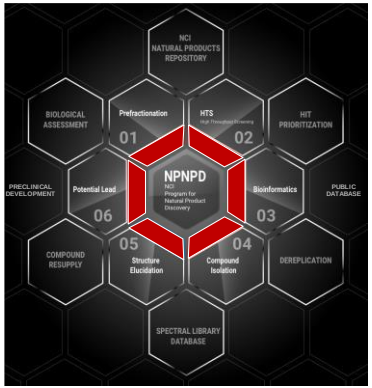
Brentuximab,
Hodgkin lymphoma

Carfilzomib
Multiple myeloma

NCI Program for Natural Products Discovery

The NCI Program for Natural Products Discovery (NPNPD) is a joint effort of the Division of Cancer Treatment and Diagnosis and the Center for Cancer Research.

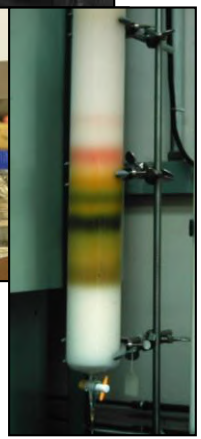


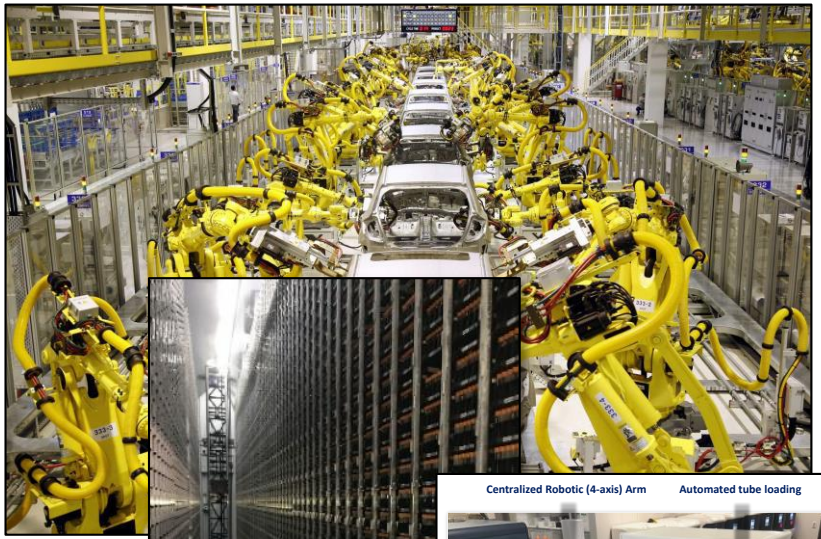


The NPNPD is designed to facilitate both intramural and extramural research and address current challenges in natural product-based drug discovery.

The NPNPD has been funded by the Cancer Moonshot Program for the years 2018-2024.

Natural Products in the 21st Century Needed a Change





NPNPD Cancer Moonshot Project Specific Aims

Aim 1. Create new technologies to build an enhanced NP pre-fractionated library amenable to modern high-throughput targeted screening programs.

Aim 2. Expand the chemical diversity available to the public from culturable microorganisms with new methods and libraries.

Aim 3. Provide the pre-fractionated library to screening centers worldwide to accelerate drug discovery.

Aim 4. Encourage high throughput screening support for researchers to enable targeted discovery efforts.

Aim 5. Provide faster analytical resources (isolation, structure elucidation, re-supply) to expedite translational pipelines.

Aim 6. Establish a public database and bioinformatics platform to broaden input and expand impact.

NPNPD Pre-fractionation Progress

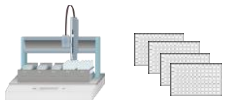
- >530,000 natural product fractions have been produced
- First 500,000 fractions released to the public
- 20-25 compounds/fraction – 10,000,000 compound library
- >25,000,000 wells of fractions plated in 384-well plates for shipping and stored in repository
- >40 research agreements executed with screening centers
- >5,000,000 samples shipped to screening centers worldwide
- Initial publications on:
  - library and methods [Thornburg *et al.* ACS Chem. Biol. 2018]
  - use for screening [Wilson *et al.* Nat Prod. Rep. 2020]
- Adoption of NPNPD methods and automated systems by research groups in U.S. (MI, MS, VA, CA), S. Africa and Sweden

Provide Faster Analytical Resources to Expedite Translation

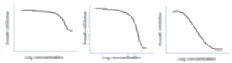
- Created an automated 2nd stage chromatography system that processes >500 samples, producing >10,000 highly pure sub-fractions, in 2 weeks
- Significantly improves speed and efficiency of “hit” confirmation by screening laboratories
- Generates valuable chemical information to annotate active samples in NCI repository
- Reduces cost and creates timelines amenable to high-throughput screening
- Conserves extracts (1 mg instead of 1g - all that is necessary for most projects)

1. ASSAY

Generation of plates

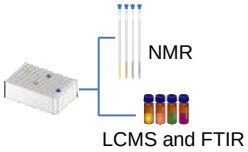


Assay data



2. DEREPLICATION

Repeat plates



Analytical data on active wells

3. ACTIVE PRINCIPLES

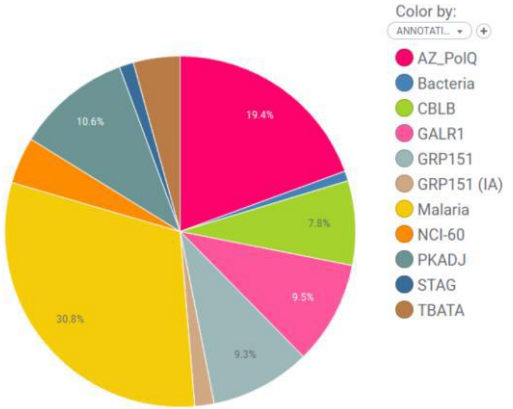
Method: **^{1}H NMR spectroscopy**
Value: High throughput, fast and comprehensive.

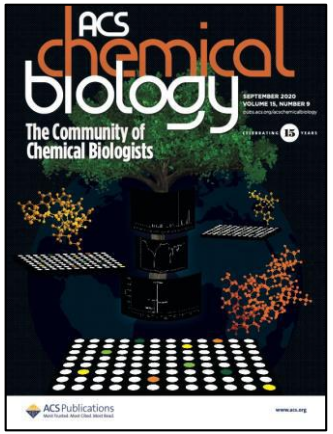
Method: **Mass spectrometry**
Value: Sensitive, high throughput.

Method: **FTIR spectroscopy**
Value: Small footprint, large spectral range.

NPNPD High Throughput Compound Isolation and Identification

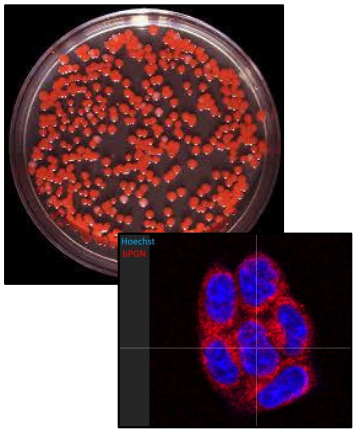
- Completed projects with WRAIR/DOD, Astra Zeneca, MTP/CCR, Baylor Med. School, NIAID, and Univ. Texas San Antonio
- >70,000 purified sub-fractions produced
- ~80-90% recovery of activity after secondary purification
- An average of >70% of active compound classes can be determined after single automated sub-fractionation
- Requires significantly less time (1 month instead of 2 yrs) and at reduced cost (2% of previous cost)
- **For ~80% of active fractions the crude extract did not show activity in the same assay – hidden chemical diversity**
- Results and methods published in 2020 [Grkovic, et al. ACS Chem. Biol. 2020]

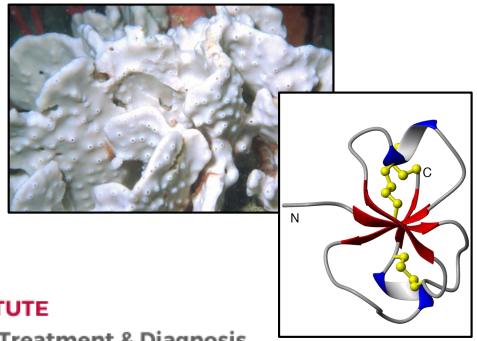


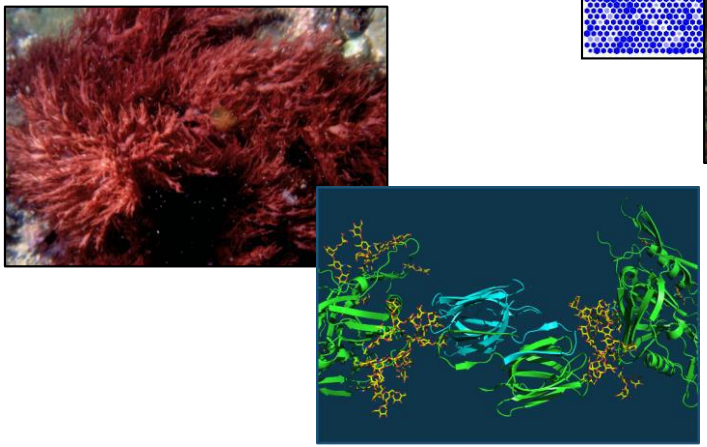


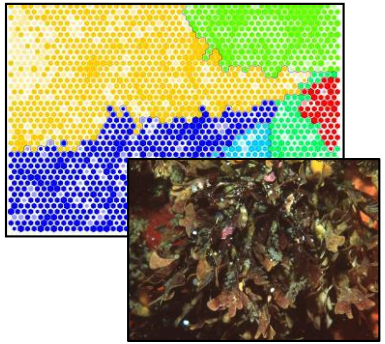
Recent Outcomes from NCI Natural Product Discovery Efforts

- DSF screen for modulators of pre-miR-21 stability
- Identification of allosteric inhibitor of TDP1
- Bioinformatic analysis to identify novel natural products
- Clinical development of the antiviral protein griffithsin



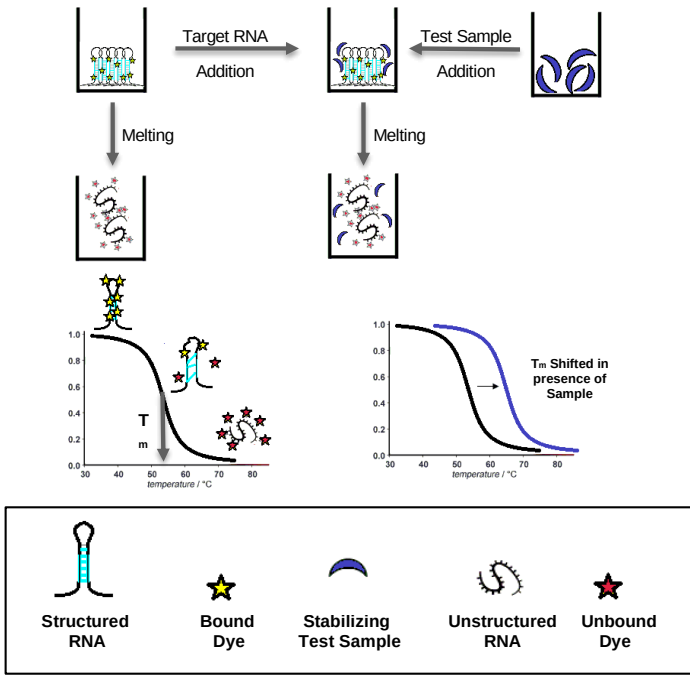




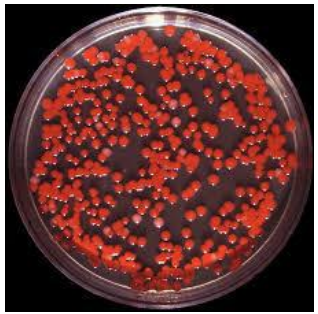


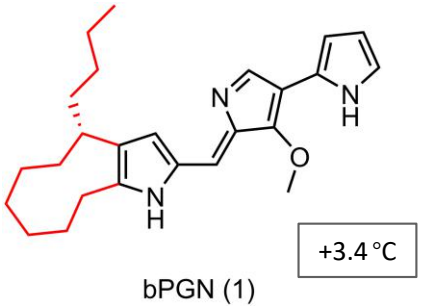
Biophysical Assays for Natural Products that Alter Macromolecular Stability

Basis of Differential Scanning Fluorimetry Assay



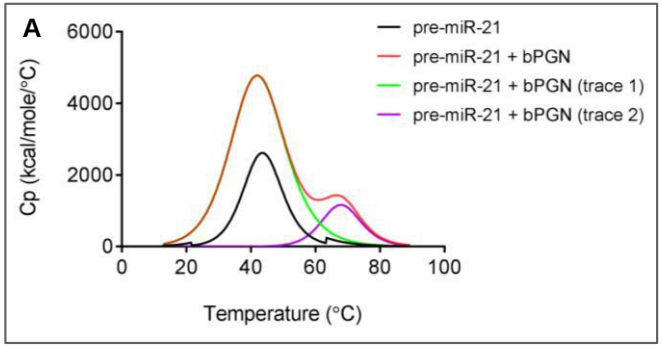
- DSF assay detects both the stabilization and destabilization of macromolecules
- Never used previously with natural product extract samples
- Reduced to practice as a high-throughput assay
- 384-well plates, 650 measurements/well
- Identified a natural product from *Serratia marcescens* that stabilizes pre-miR-21

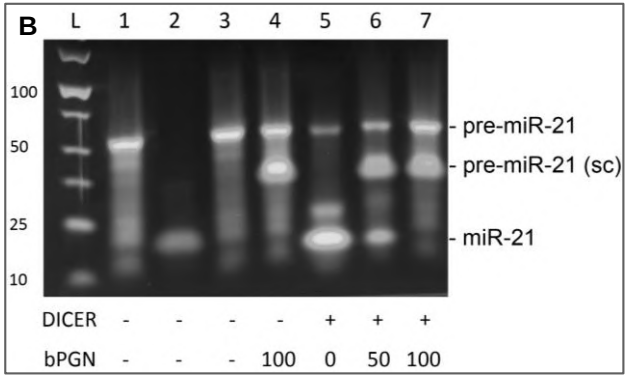


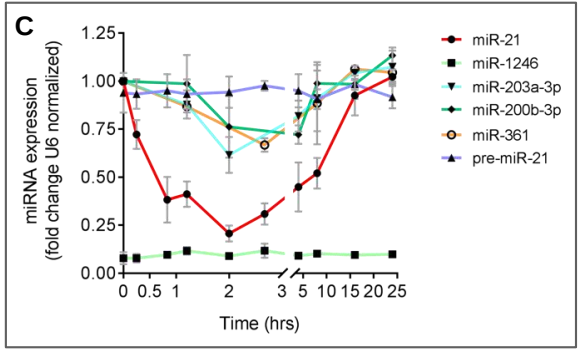


bPGN (1)

Discovery of pre-miR-21 Modulating Natural Products







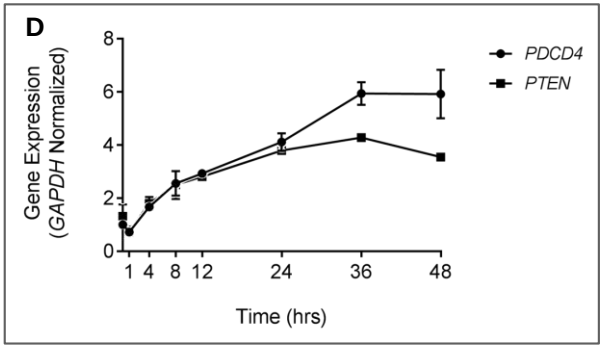
A. bPGN stabilizes pre-miR-21

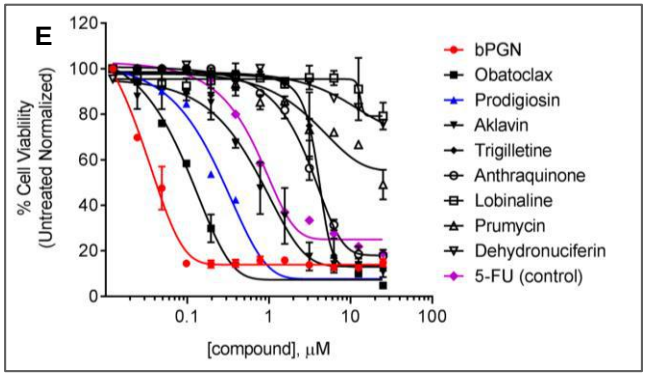
B. bPGN induces a second, supercoiled form of pre-miR-21

C. miR-21 levels are reduced in the cell

D. Reduction in miR-21 causes PDCD4 and PTEN levels to increase

E. HCT116 cells die as a result of treatment with bPGN

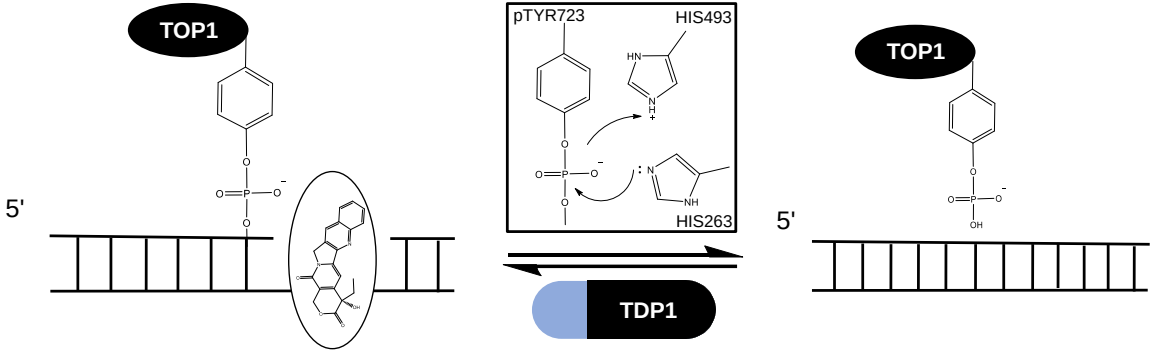


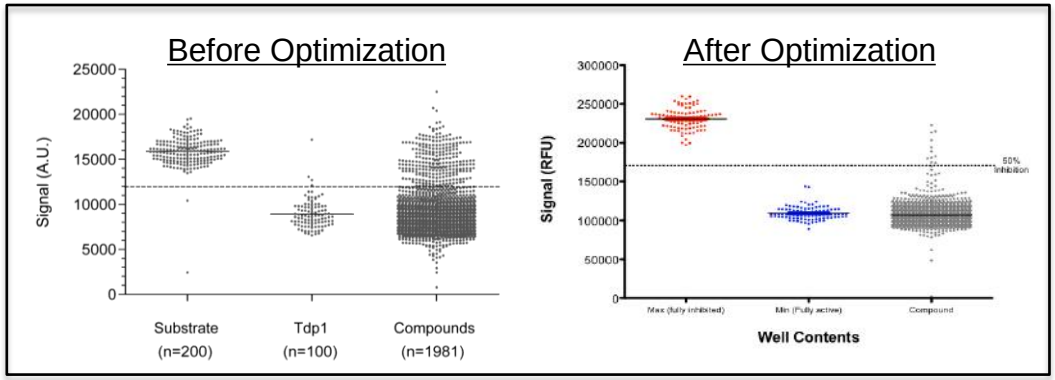


Matarlo, et al. *Cell Chem. Biol.* 2019.

Screen for Inhibitors of Tyrosyl-DNA Phosphodiesterase 1

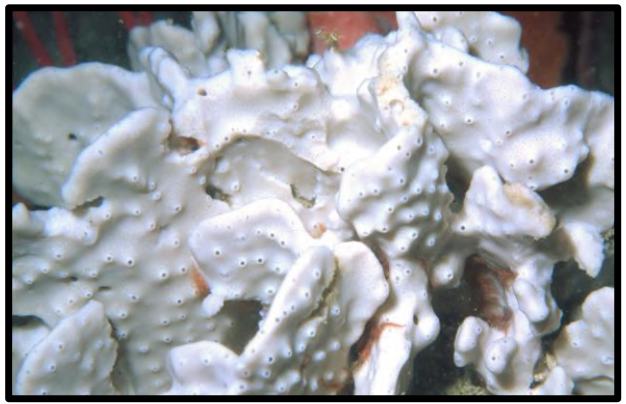
- TDP1Hydrolyzes covalent bond between tyrosine of Top I and 3’ end of DNA
- TDP1 reverses Topoisomerase I inhibition (repairs stalled complex)
- MTP created an assay that replaced tyrosyl moiety with a fluorescent molecule
- Assay was optimized for use with natural product samples
- Fractionated natural product hit rate was ~0.3%





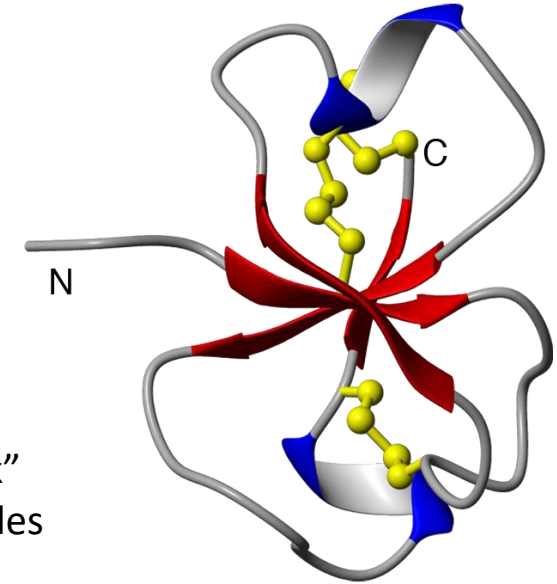
Bermingham, *et al*. *SLAS Disc.* 2017.

Novel Peptide Inhibitor of Tyrosyl-DNA Phosphodiesterase 1

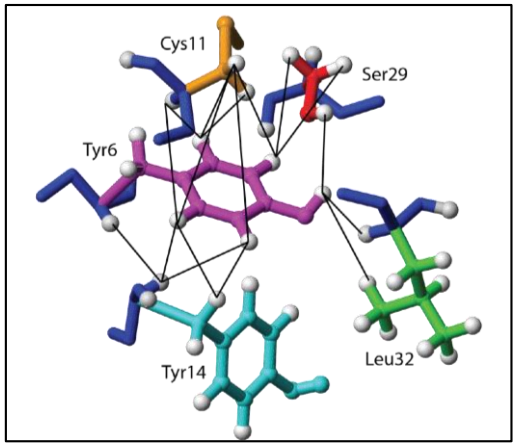


Recifin A

- Recifin A is a novel peptide from the sponge *Axinella* sp.
- Inhibits TDP1 with a Ki of 190 nM
- Has a unique disulfide bonding pattern
- Is a completely new class of "Tyr-Lock" peptide structure distinct from cyclotides

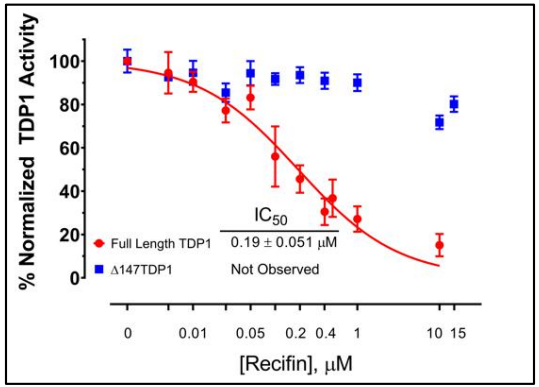


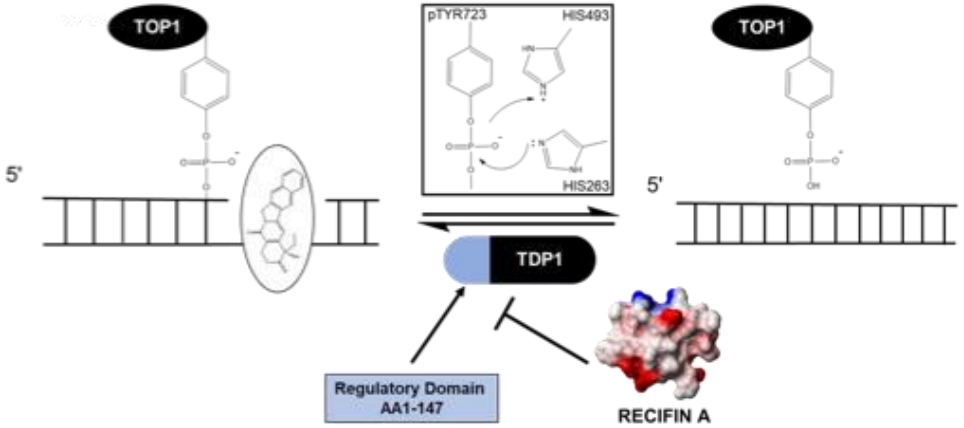
For José!



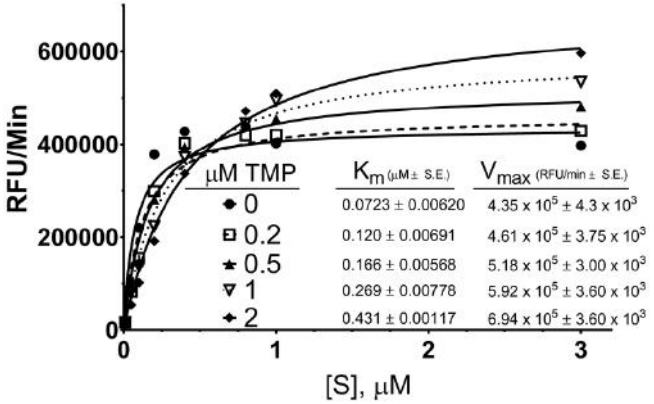
Krumpe, *et al*. *J. Am. Chem. Soc.* 2020.

Allosteric Inhibition of Tyrosyl-DNA Phosphodiesterase 1





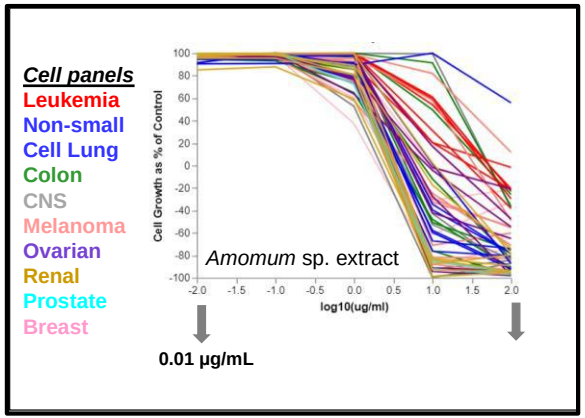
- Does not inhibit Δ147 truncated TDP1
- First 147 amino acids of TDP1 is known to be the regulatory domain (e.g. phpsphorylation, SUMOylation)
- Modulates both the Km and Vmax of TDP1
- **It is the first known allosteric inhibitor of Tdp1**

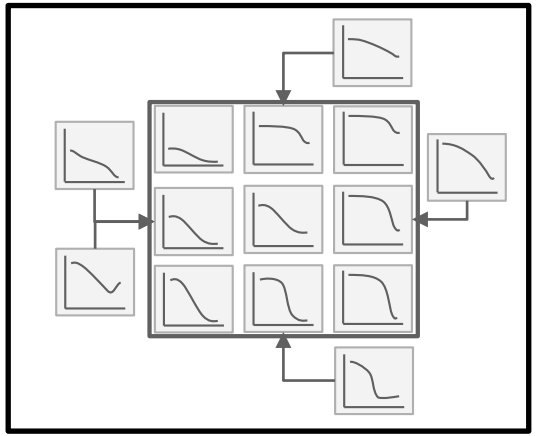


Krumpe, *et al*. *J. Am. Chem. Soc.* 2020.

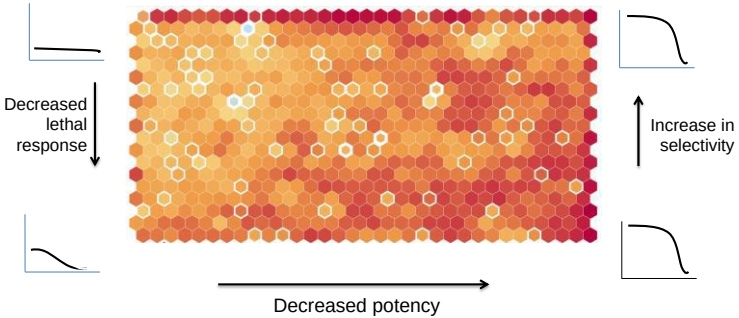
Bioinformatic Tools to Drive Anti-cancer Drug Discovery

- Based on self-organizing-map analysis of NCI-60 cytotoxicity data developed as part of the NPNPD
- Compares pattern of NCI-60 cell line cytotoxicity curves (300 data points/sample)



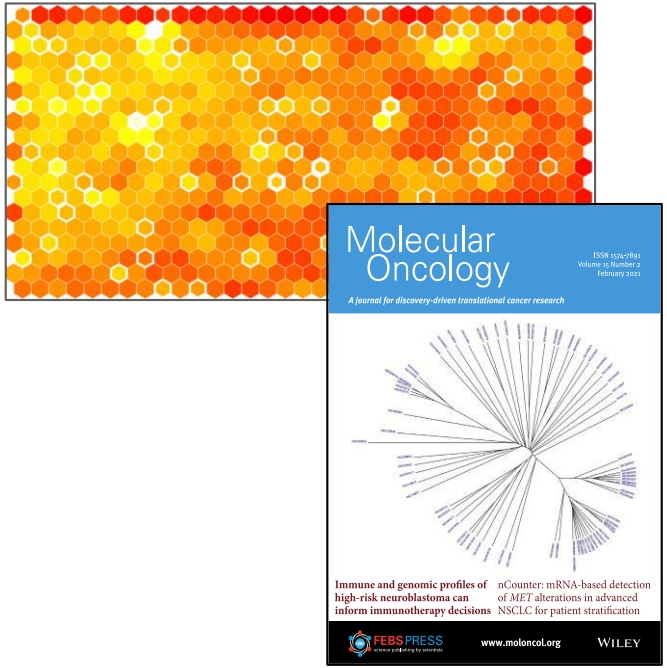


For Osvaldo!



Bioinformatic Tools to Drive Anti-cancer Drug Discovery

- SOM data insufficient for prediction; needed to add another dimension to the data
- Initial project re-parsed NCI-60 activity profiles for >1400 natural products by the “genetic signature” of the cell lines to identify correlations with specific mutations/expression levels/SNPs etc.
- The methodology has now been used for ~140,000 records for natural products extracts to predict potential mechanisms for active extracts from NCI-60 data files



Krushkal *et al. Mol. Oncology, 2021*

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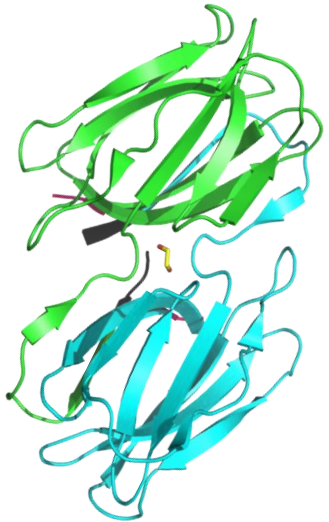
Joe Matarlo*

Center for Cancer Reserch
Joel Schneider (CBL)
Yves Pommier (DTB)
Christina Schroeder (CBL)
Ping Zhang (CBL)

* alumni

The Antiviral Protein Griffithsin (GRFT)

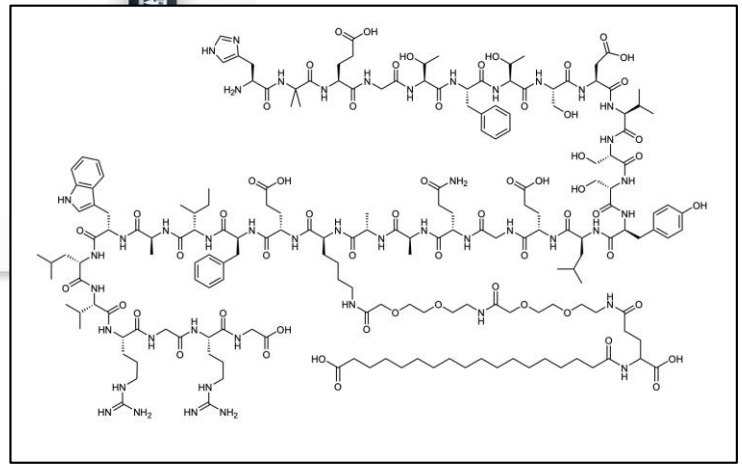
- Protein isolated in the Molecular Targets Program (MTP/NCI) from an extract of the red alga *Griffithsia* sp. collected in New Zealand
- 12.7 kDa monomer, obligate domain-swapped homodimer
- No homology to any previously reported protein
- Active against all clades of HIV at picomolar concentrations
- Binds to HIV-1 envelope glycoproteins
- Readily expressed and purified from recombinant systems
- Very stable (melting temp. = ~78°C), stable to organic solvents, resistant to proteases



Clinically-approved Biotherapeutics from Natural Sources

H–His–Gly–Glu–Gly–Thr–Phe–Thr–
Ser–Asp–Leu–Ser–Lys–Gln–Met–
Glu–Glu–Glu–Ala–Val–Arg–Leu–
Phe–Ile–Glu–Trp–Leu–Lys–Asn–
Gly–Gly–Pro–Ser–Ser–Gly–Ala–
Pro–Pro–Pro–Ser–NH_2

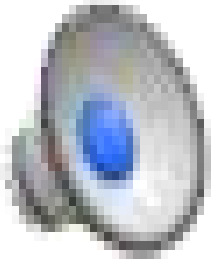
For Ana!

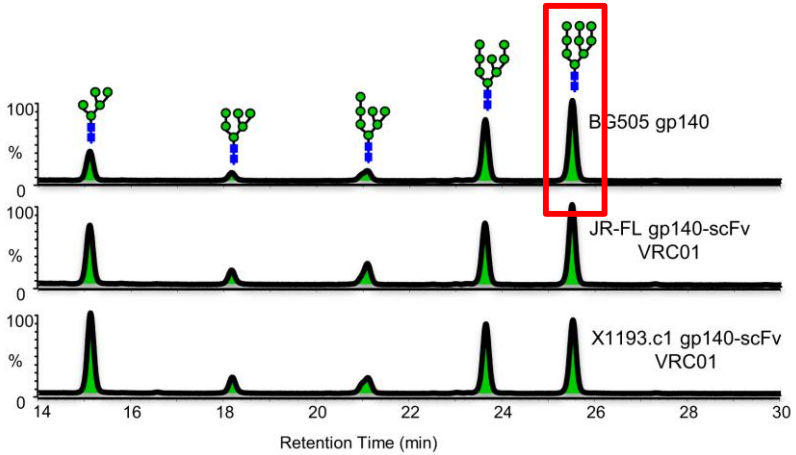


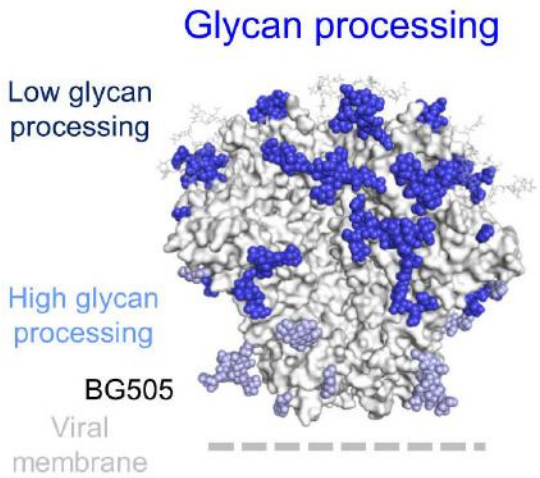
Derived from a hormone found in Gila monster saliva

- Glucagon-like peptide agonist
- New version approved in 2021 for the treatment of obesity

Gp120's Glycan Shield : Immune Response Evasion and GRFT Binding Targets







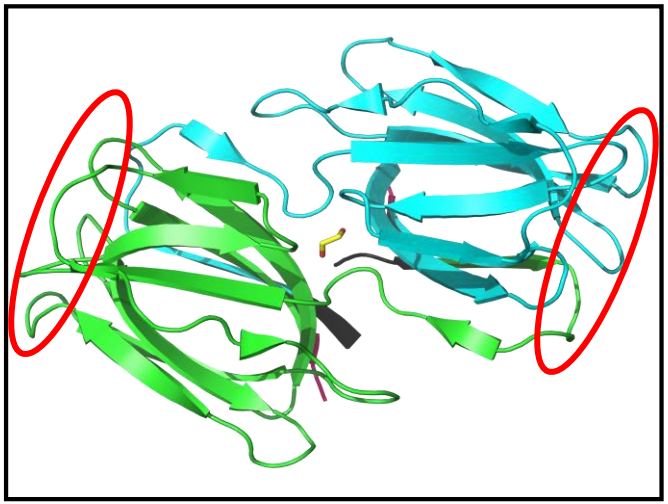
	Affinity (μM)	ΔH (kcal/mol)	ΔG (kcal/mol)	TΔS (kcal/mol)
mannose	102.0±13.0	-0.081±0.002	-5.53±0.08	5.54±0.08
1➔2α-mannobiose	53.9±6.6	-0.173±0.003	-5.91±0.07	5.74±0.07
Manno-pentaose	18.9±2.8	-1.20±0.14	-6.54±0.88	5.35±0.14
Nona-mannoside	0.50±0.16	-13.50±0.11	-8.73±0.31	-4.75±0.31
HIV-1 sgp120	0.008±0.004	-30.40±0.26	-11.20±0.28	-19.16±0.28

NIH NATIONAL CANCER INSTITUTE
Center for Cancer Research

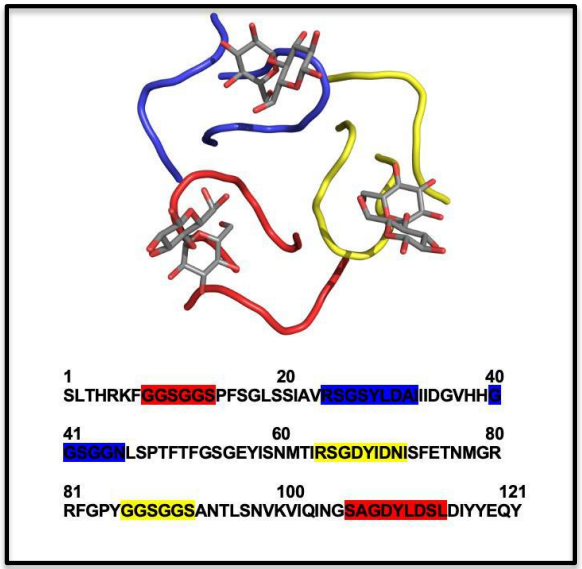
Guillaume. *et al.* Cell, 2016.

GRFT Carbohydrate Binding Interface

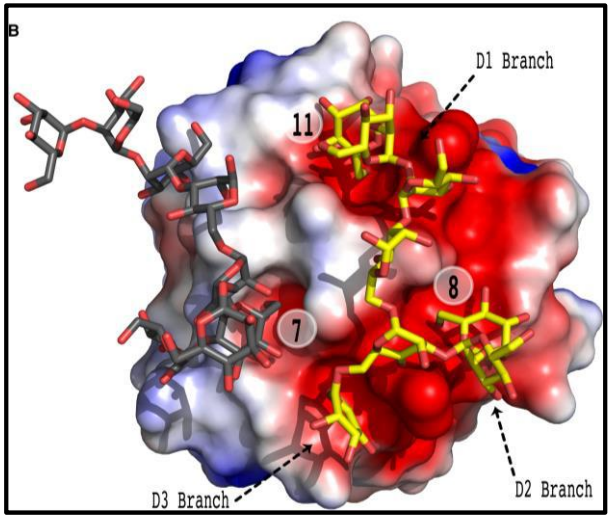
Griffithsin is an obligate homodimer



With three binding domains

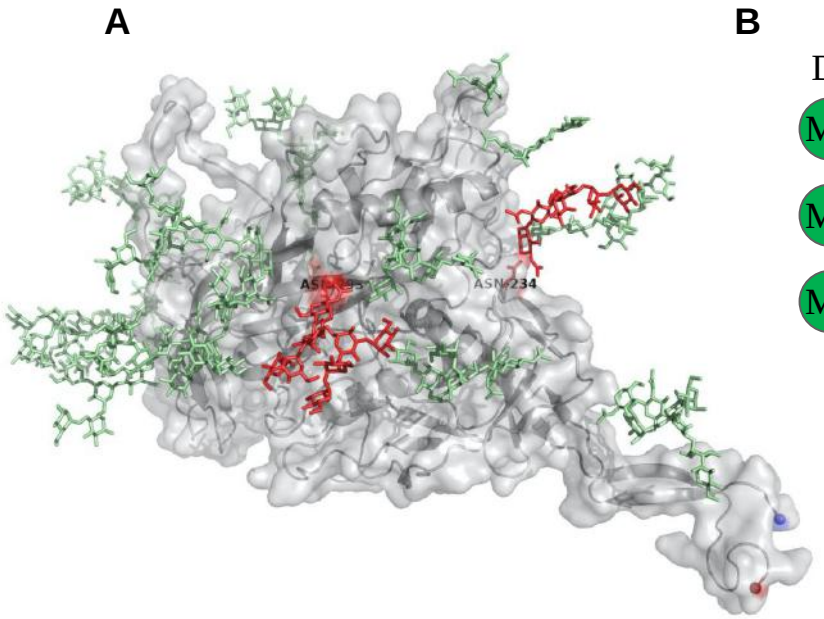


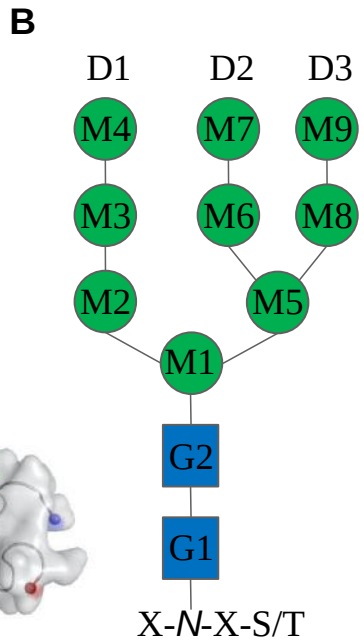
Enabling oligosaccharide crosslinking

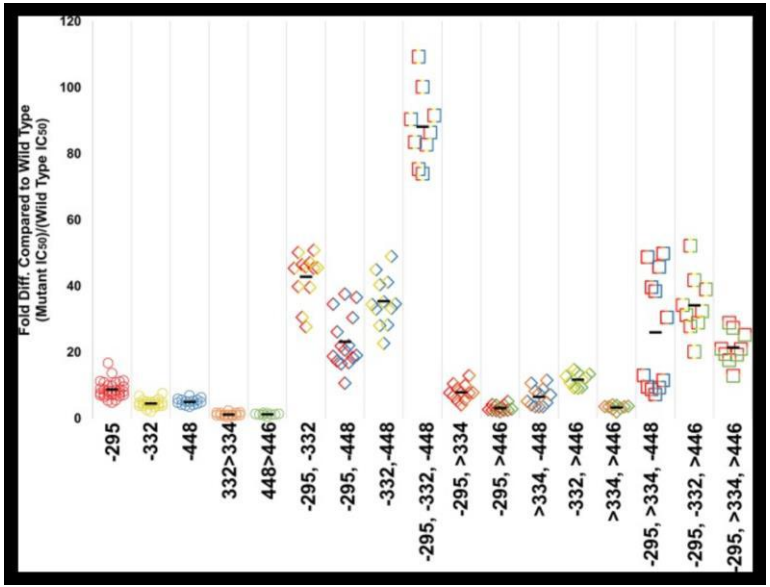


Ziółkowska, N.E. *et al. Structure, 2006; Moulaei et al. Structure, 2010*

HIV-1 Resistance to GRFT and gp120 Glycosylation







Mitchell et al. , Antiviral Res., 2017; Fischer et al., Antimicrob. Agents Chemother., 2019[24]

Development of Griffithsin as an Anti-HIV Microbicide

Two Groups have brought GRFT to Phase I Clinical Trials

The Population Council (funded by USAID)

POPULATION COUNCIL
Ideas. Evidence. Impact.

Brought vaginal GRFT/Carrageenan gel (PC-6500) to trial in 2018.
Also developing vaginal ring and fast dissolving tablets.

Intrucept Biomedicine and University of Louisville (funded by NIAID)

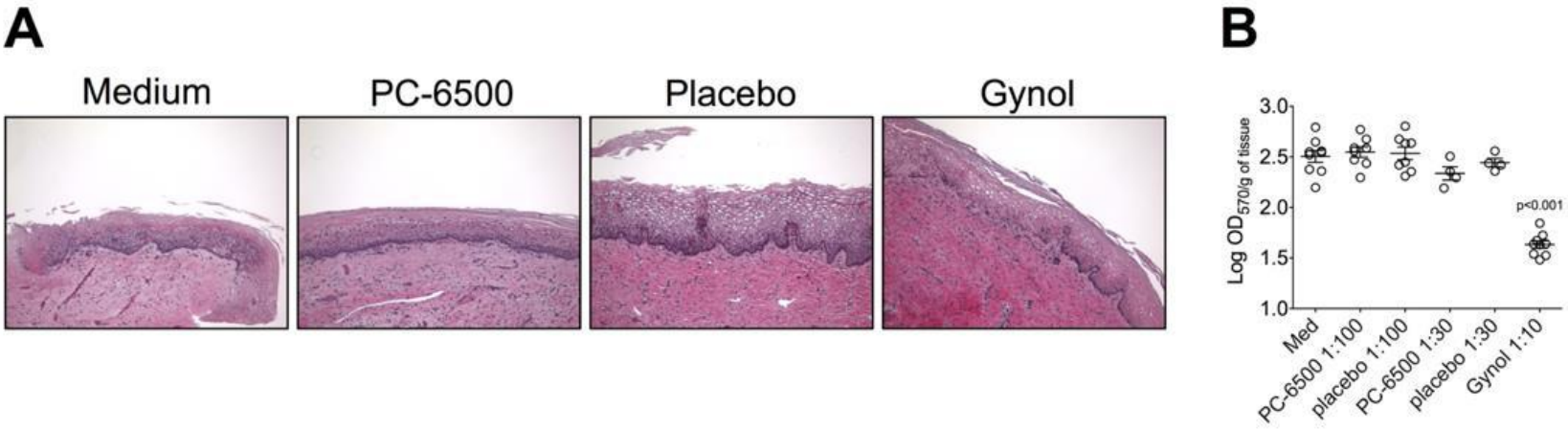
Q-GRFT PREVENT

Brought Q-GRFT enema to trial in 2020.
Using new oxidation-resistant GRFT analog

Phase 1 Trial to Assess Safety, PK & PD of GRFT gel (PC-6500)

- **Rationale:** Testing vaginal gel formulation of GRFT to inform FDI and IVR development
- **Design:** Randomized, placebo-controlled (2:1), double-blind 14d period, preceded by single-dose, open label period
- **Products:** PC-6500 (0.1% GRFT gel) and CG placebo
- **Population:** 36 healthy, abstinent females, 18-49
- **Site:** Albert Einstein College of Medicine, Bronx, NY (Marla Keller, PI)
- **Trial completed in 2018, results published in 2022**

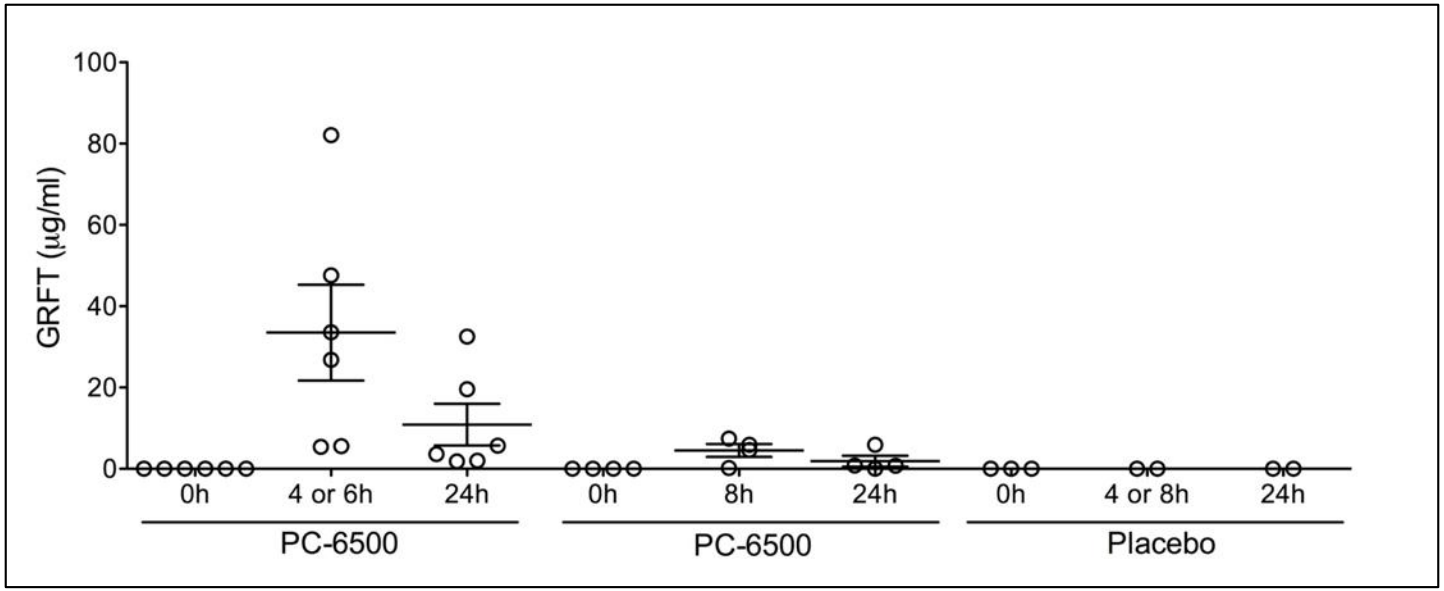
PC-6500 GRFT gel Effect on Human Ectocervical Explants



PC-6500 is not toxic to human ectocervical mucosa. **(A)** Polarized human ectocervical explants were cultured for ~18h in the presence of neat gels vs. medium applied on the epithelium (single explant/condition). To assess epithelial integrity after exposure to the gels, tissues were washed, paraffin-embedded, and stained with H&E. Representative of at least 3 experiments is shown. **(B)** Alternatively, tissues were immersed in medium containing diluted PC-6500 (vs. medium, diluted placebo and Gynol controls)

Teleshova et al., PLoS ONE, 2022

PC-6500 GRFT Levels Above EC_{50} 4-6 hrs Post-administration



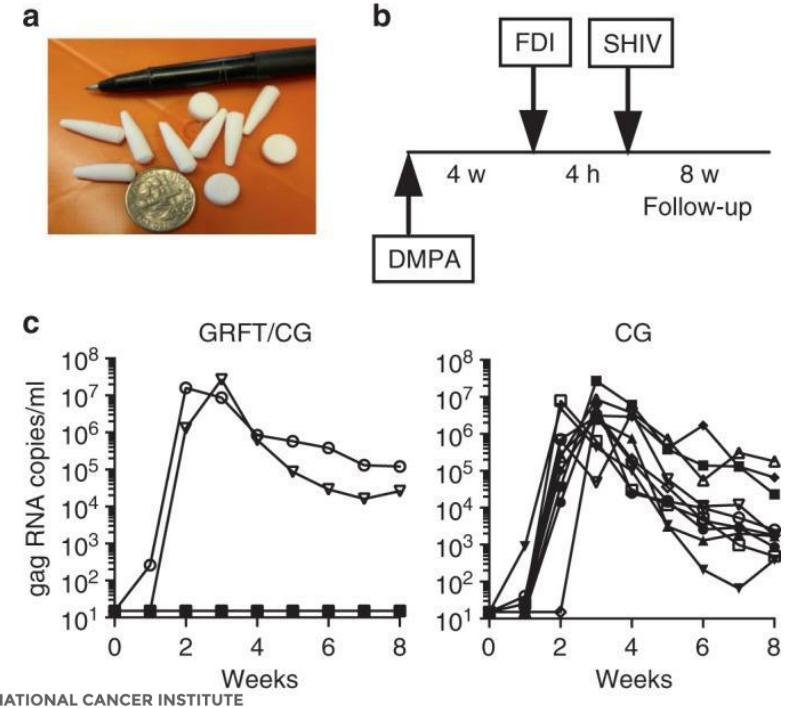
GRFT concentrations in CVL from participants in the randomized phase. GRFT concentrations (Mean ± SEM) 4h (or 6h) or 8h after single gel application and 24h after last gel application.

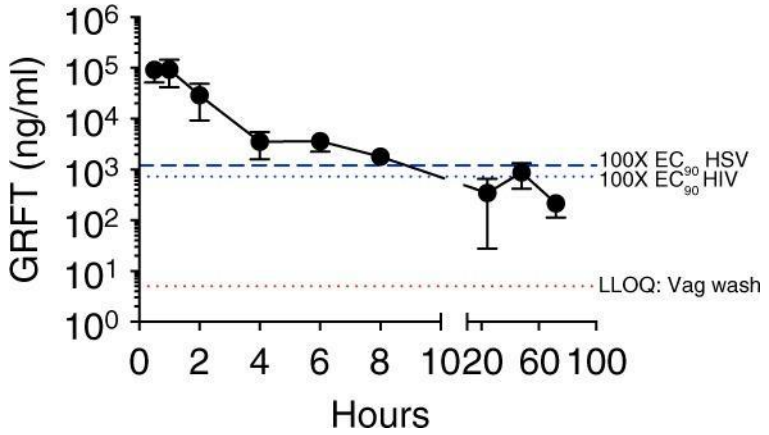
CVLs from study participants protective against HIV at 4 & 6 hr timepoints but not at 24 hr timepoint

Teleshova et al., PLoS ONE, 2022

Fast Dissolving Insert Formulation of GRFT

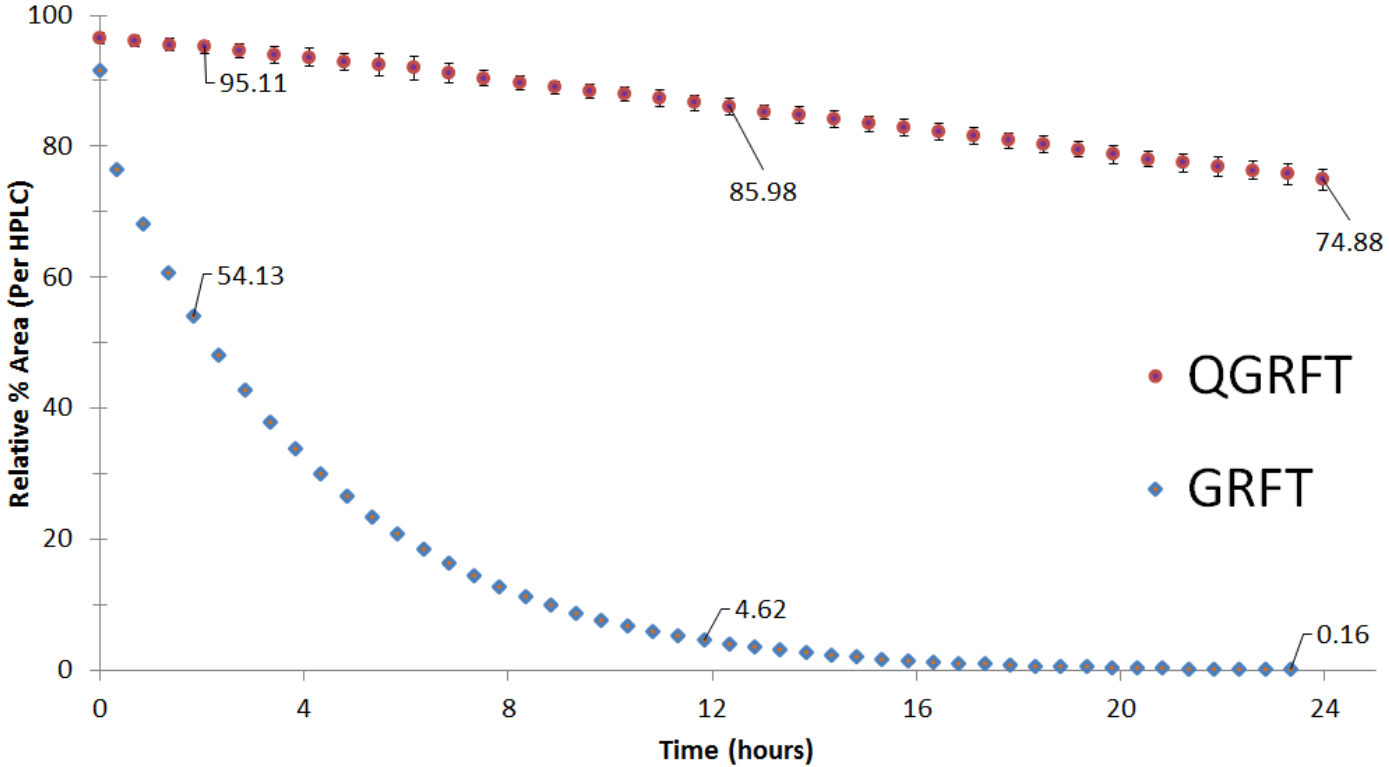
- GRFT/CG formulated into a fast-dissolving insert (dissolves in 90 sec)
- Protects animals from three different viral infections in (SHIV, HSV-1, HPV) up to 8hrs
- NIAID- funded grant to for continued development toward the clinic





Derby, *et al.* Nat. Commun., 2018.

Comparison of GRFT and Q-GRFT Oxidation (with 0.02% H_2O_2, 40°C)

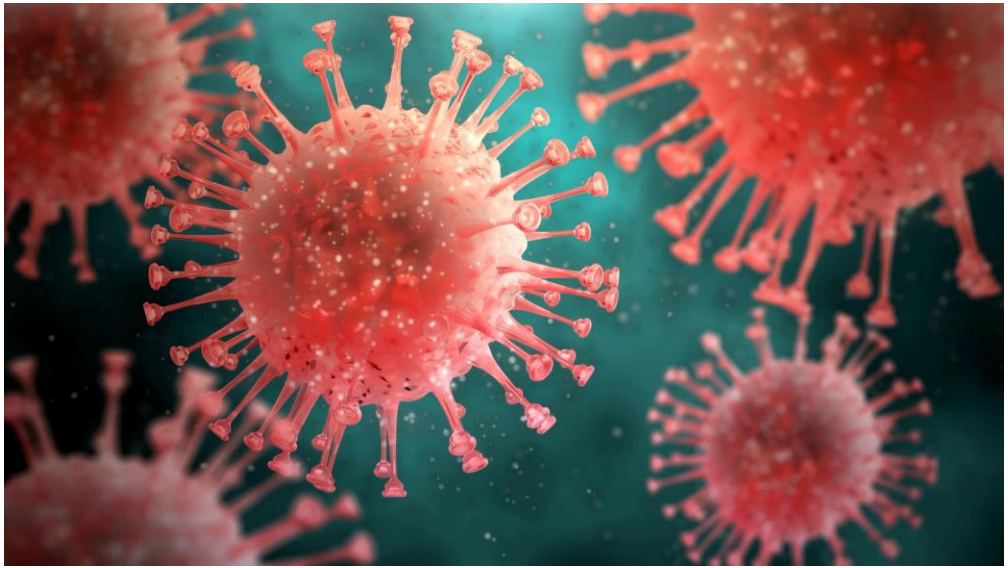


Krazmer et al., AAPS PharmSciTech, 2021

Q-GRFT Enema Clinical Trial (Q-GRFT PREVENT)

- **Rationale:** Testing rectal enema formulation of Q-GRFT for potential use in prevention of HIV
- **Design:** Randomized, placebo-controlled (2:1), double-blind single dose, preceded by single-dose, open label period
- **Products:** 40 mg GRFT enema and placebo
- **Population:** Up to 21 healthy individuals between 18-45
- **Site:** University of Pittsburgh Medical Center- Magee-Women's Hospital, Pittsburgh, PA (PI: Rhonda Brand)
- **Trial completed in 2020, terminated early (18 participants) due to reaching statistical significance when reviewed during COVID-19 related pause; no drug-related adverse events reported**

GRFT and a Virus Family of More Recent Concern



Griffithsin Activity Against SARS-CoV-1

JOURNAL OF VIROLOGY, Mar. 2010, p. 2511–2521 Vol. 84, No. 5
0022-538X/10/$12.00 doi:10.1128/JVI.02322-09

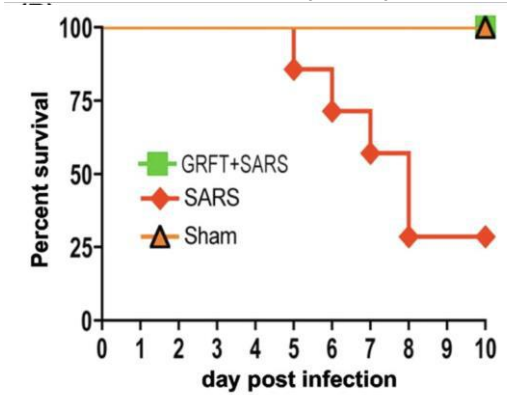
Broad-Spectrum *In Vitro* Activity and *In Vivo* Efficacy of the Antiviral Protein Griffithsin against Emerging Viruses of the Family *Coronaviridae*▽

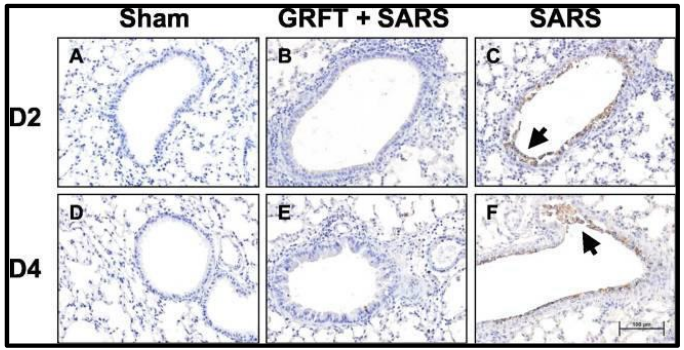
Barry R. O'Keefe,[1]* Barbara Giomarelli,[1] Dale L. Barnard,[2] Shilpa R. Shenoy,[3] Paul K. S. Chan,[4] James B. McMahon,[1] Kenneth E. Palmer,[5,6] Brian W. Barnett,[5] David K. Meyerholz,[7] Christine L. Wohlford-Lenane,[7] and Paul B. McCray, Jr.[8,9]*

GRFT activity against coronaviruses (cytopathicity assay)

Coronavirus	Strain	EC_{50} (μg/ml)	IC_{50} (μg/ml)	Selectivity Index
SARS-CoV	Urbani	0.61	>100	>164
	Tor-II	0.61	>100	>164
	CuHK	0.78	>100	>128
	Frank	1.19	>100	>83
HCoV	OC43	0.16	52	325
	229E	0.18	>79	>56
	NL63	<0.0032	>79	>3100

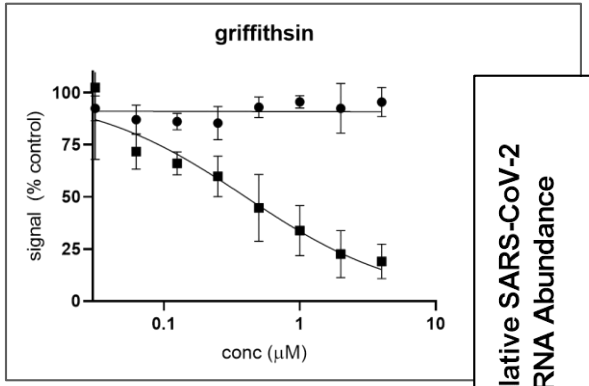
GRFT Activity Against SARS-CoV in MICE following Intranasal Administration (pre-exposure)

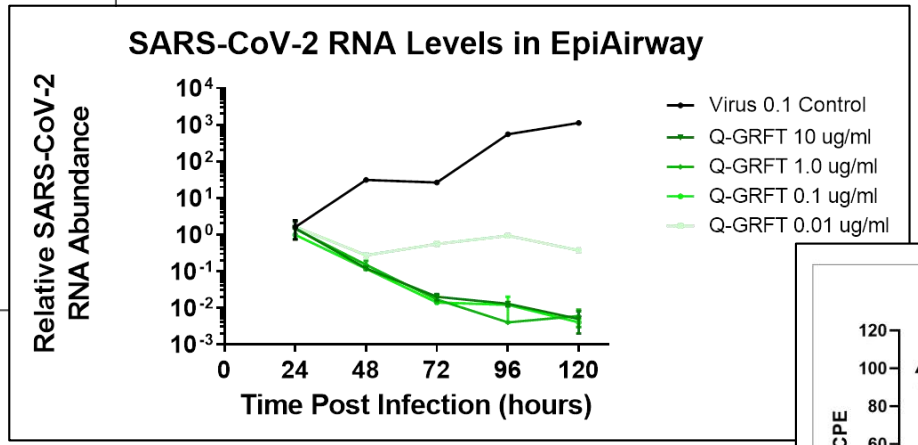


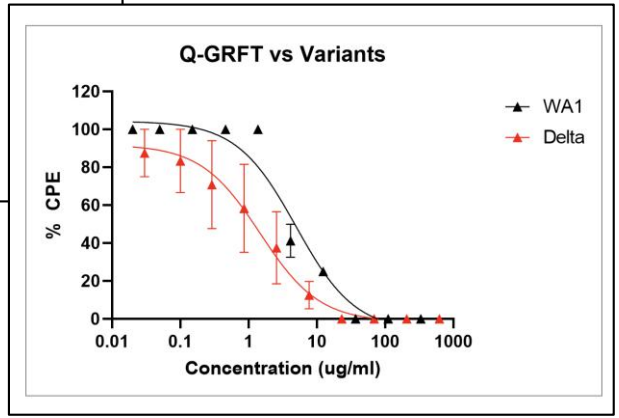


In Vitro Activity of GRFT and Q-GRFT Against SARS-CoV-2

- GRFT was active in inhibiting SARS-CoV-2 pseudovirus viral entry
- Q-GRFT reduced viral titers in a EpiAirway model
- Delta strain more sensitive than original Wuhan strain

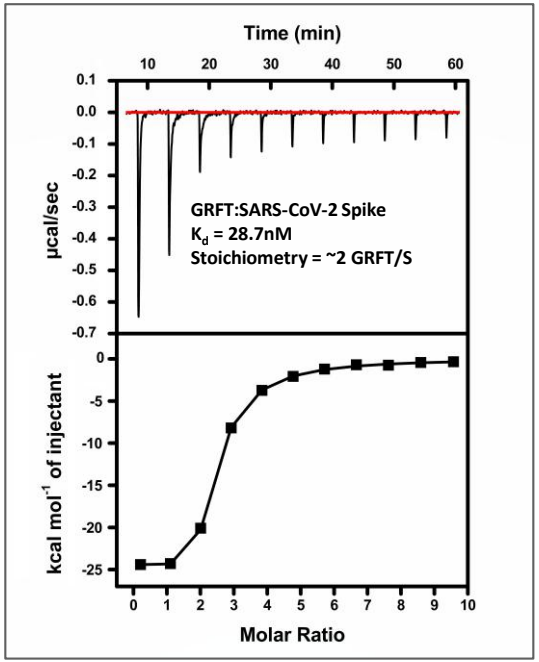


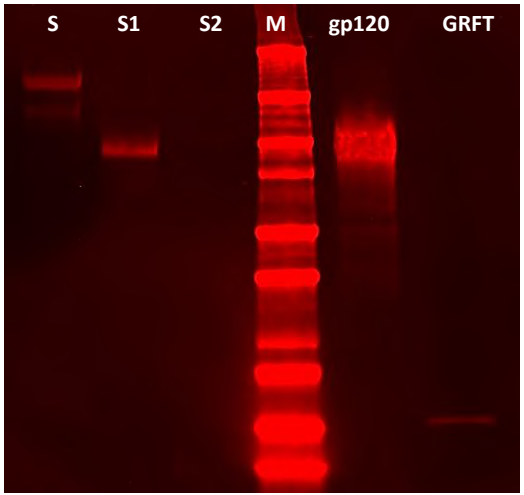


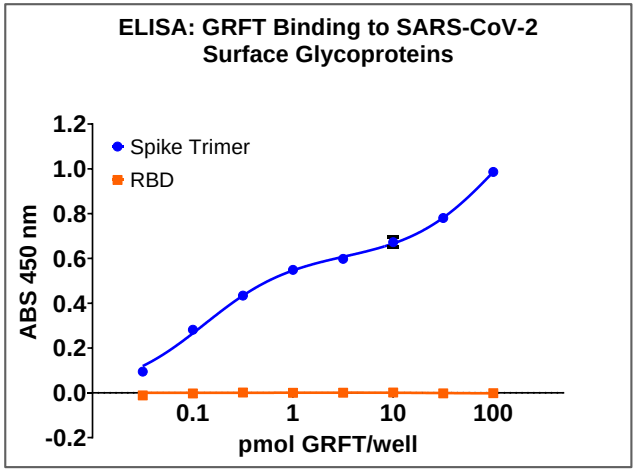


GRFT Binding to SARS-CoV-2 Spike Glycoprotein

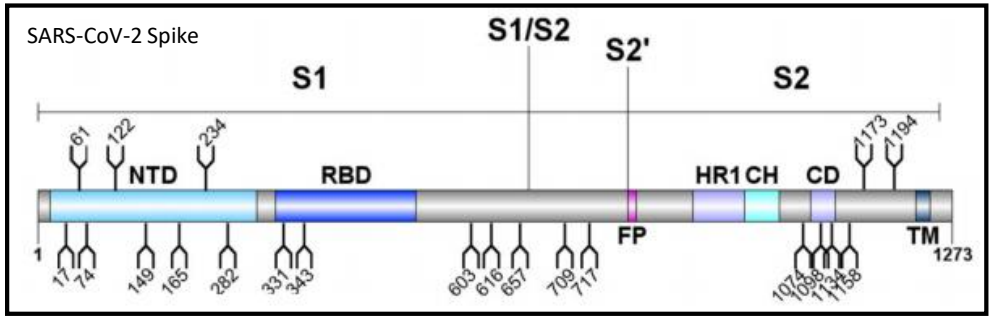
- Isothermal titration calorimetry was performed on GRFT and SARS-CoV-2 Spike
- Western Blot of furin-cleaved Spike separated into S1 and S2 regions
- ELISA studies on GRFT binding to the receptor binding domain (RBD) of Spike



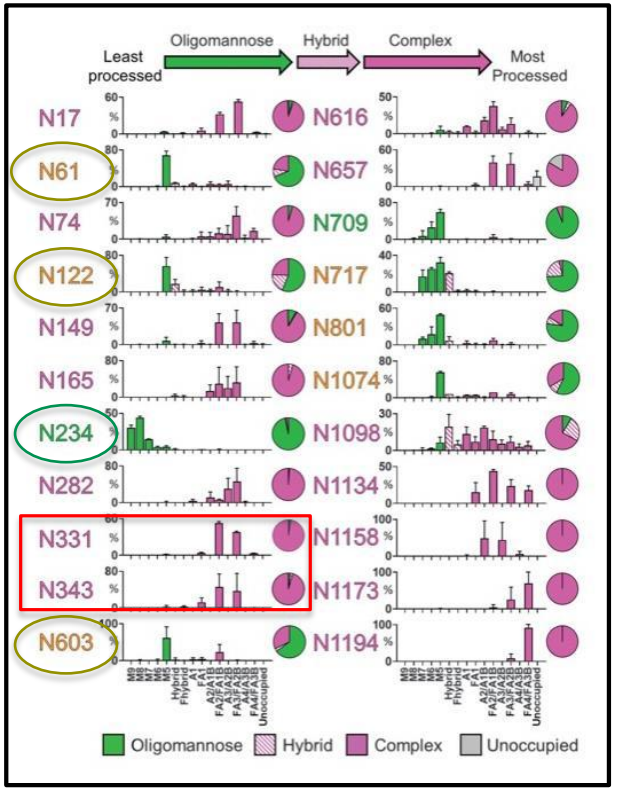




GRFT and SARSCoV-2 Spike Glycoprotein Glycosylation

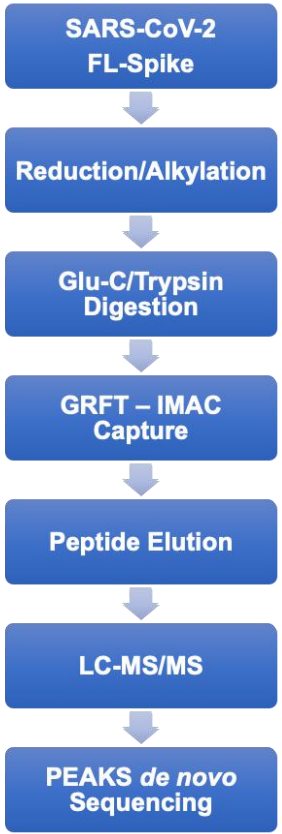


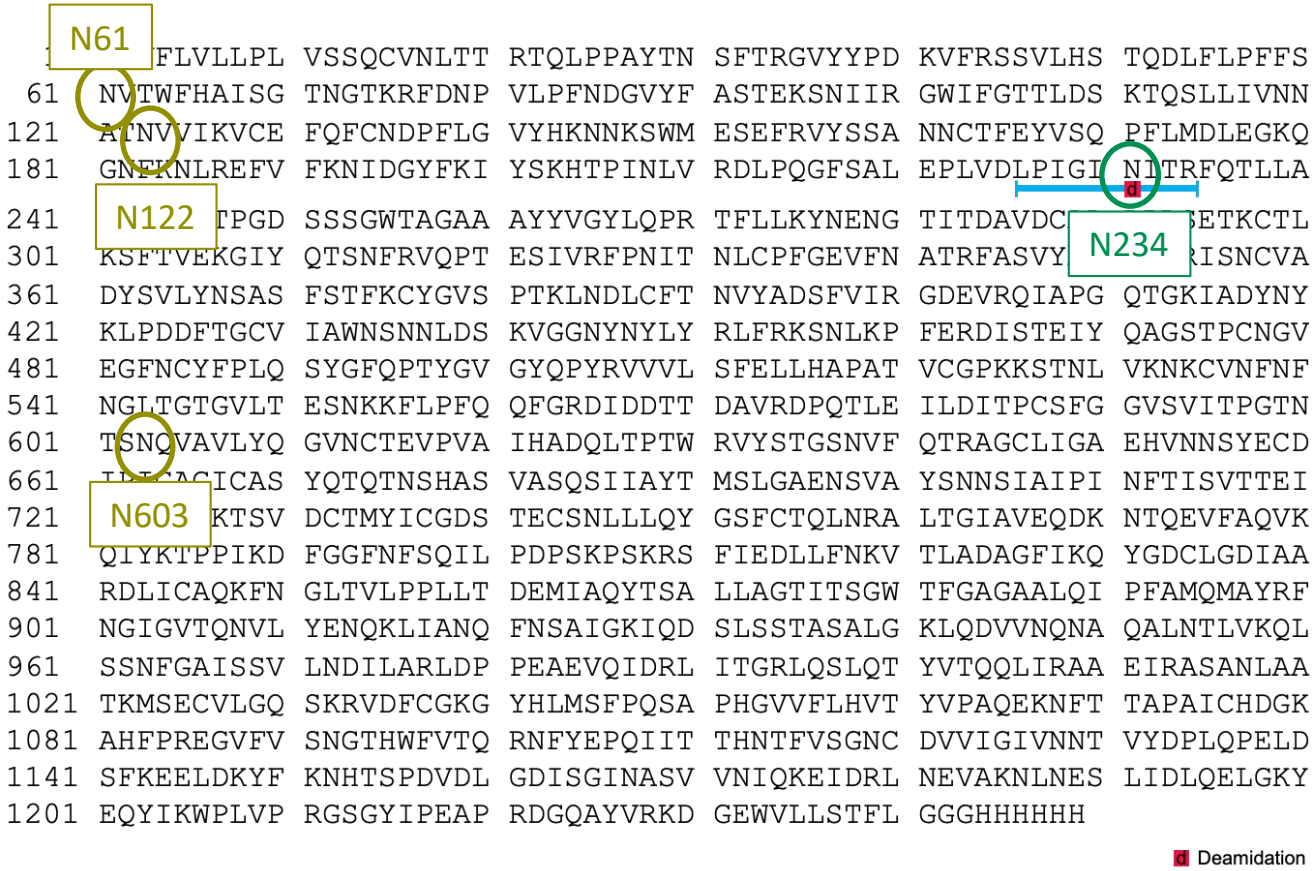
- SARS-CoV-2 Spike glycoprotein (S) has 22 N-linked oligosaccharides, two on the receptor binding domain (RBD) at positions
- 32% of total glycans are oligomannose oligosaccharides (green) but RBD oligosaccharides are complex (pink) - N331 & N343
- GRFT binds only to high mannose oligosaccharides
- GRFT has two binding sites to Spike in the S1 domain (AA1-681) but does not bind to the RBD of SARS-CoV-2



Watanabe *et al*. Science, 2020

Identifying GRFT Binding Sites on SARS-CoV-2 Spike

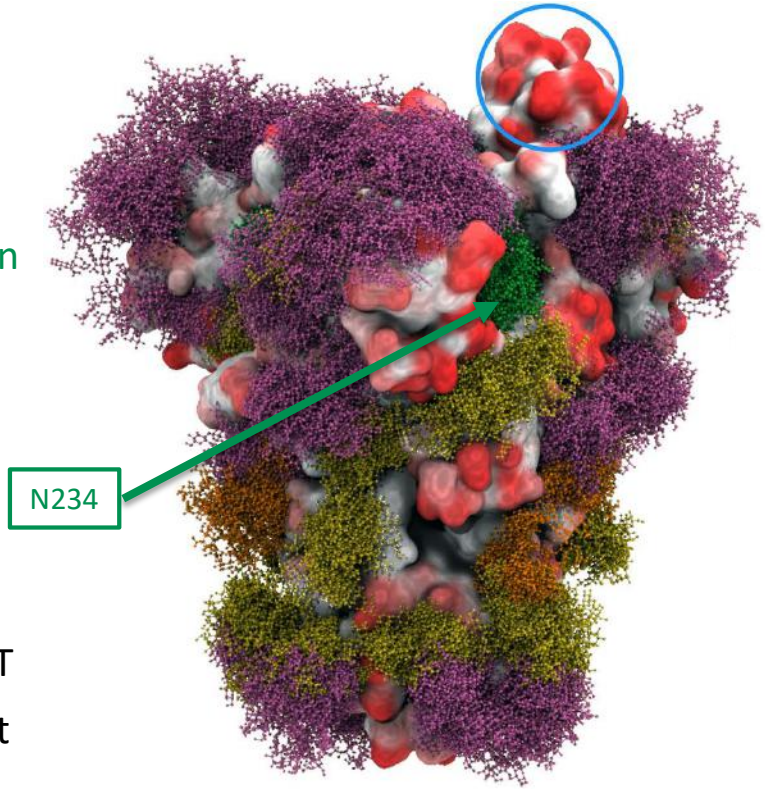





```
   1  FLVLLPL VSSQCVNLTT RTQLPPAYTN SFTRGVYYPD KVFRSSVLHS TQDLFLPFFS
  61  NVTWFHAISG TNGTKRFDNP VLPFNDGVYF ASTEKSNIIR GWIFGTTLDS KTQSLLIVNN
 121  ATNVVIKVCE FQFCNDPFLG VYHKNNKSWM ESEFRVYSSA NNCTFEYVSQ PFLMDLEGKQ
 181  GNFKNLREFV FKNIDGYFKI YSKHTPINLV RDLPQGFSAL EPLVDLPIGI NITRFQTLLA
 241  TPGD SSSGWTAGAA AYYVGYLQPR TFLLKYNENG TITDAVDC  ETKCTL
 301  KSFTVEKGIY QTSNFRVQPT ESIVRFPNIT NLCPFGEVFN ATRFASVY  ISNCVA
 361  DYSVLYNSAS FSTFKCYGVS PTKLNDLCFT NVYADSFVIR GDEVRQIAPG QTGKIADYNY
 421  KLPDDFTGCV IAWNSNNLDS KVGGNYNYLY RLFRKSNLKP FERDISTEIY QAGSTPCNGV
 481  EGFNCYFPLQ SYGFQPTYGV GYQPYRVVVL SFELLHAPAT VCGPKKSTNL VKNKCVNFNF
 541  NGLTGTGVLT ESNKKFLPFQ QFGRDIDDTT DAVRDPQTLE ILDITPCSFG GVSVITPGTN
 601  TSNQVAVLYQ GVNCTEVPVA IHADQLTPTW RVYSTGSNVF QTRAGCLIGA EHVNNSYECD
 661  IPIGAGICAS YQTQTNSHAS VASQSIIAYT MSLGAENSVA YSNNSIAIPI NFTISVTTEI
 721  KTSV DCTMYICGDS TECSNLLLQY GSFCTQLNRA LTGIAVEQDK NTQEVFAQVK
 781  QIYKTPPIKD FGGFNFSQIL PDPSKPSKRS FIEDLLFNKV TLADAGFIKQ YGDCLGDIAA
 841  RDLICAQKFN GLTVLPPLLT DEMIAQYTSA LLAGTITSGW TFGAGAALQI PFAMQMAYRF
 901  NGIGVTQNVL YENQKLIANQ FNSAIGKIQD SLSSTASALG KLQDVVNQNA QALNTLVKQL
 961  SSNFGAISSV LNDILARLDP PEAEVQIDRL ITGRLQSLQT YVTQQLIRAA EIRASANLAA
1021  TKMSECVLGQ SKRVDFCGKG YHLMSFPQSA PHGVVFLHVT YVPAQEKNFT TAPAICHDGK
1081  AHFPREGVFV SNGTHWFVTQ RNFYEPQIIT THNTFVSGNC DVVIGIVNNT VYDPLQPELD
1141  SFKEELDKYF KNHTSPDVDL GDISGINASV VNIQKEIDRL NEVAKNLNES LIDLQELGKY
1201  EQYIKWPLVP RGSGYIPEAP RDGQAYVRKD GEWVLLSTFL GGGHHHHHH
```

N234 Oligosaccharide and SARSCoV-2 Spike Glycoprotein

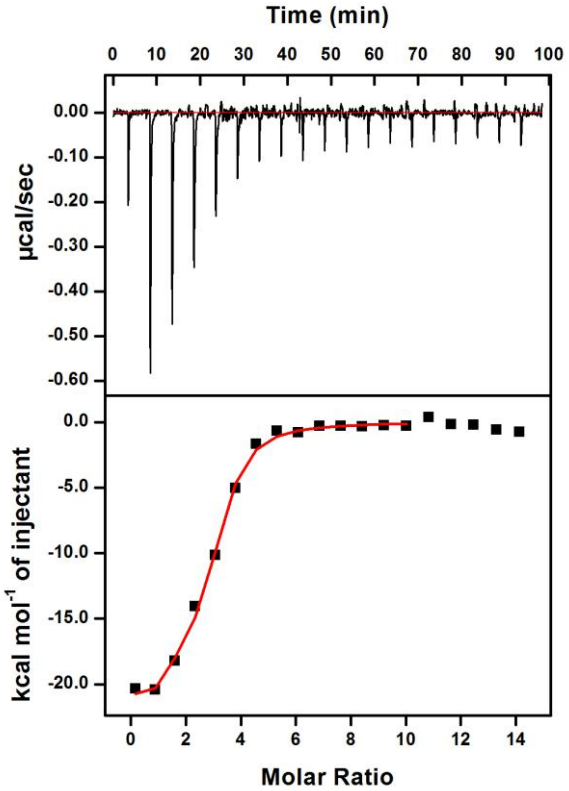
- SARS-CoV-2 Spike complex oligosaccharides shown in purple
- Oligomannosides are shown in light green
- N234 high mannose oligosaccharide shown in dark green
- N234 oligosaccharide has been shown in Cryo-EM studies to stabilize the RBD enabling viral entry
- Mutation to omit N234 oligosaccharide results in 40% reduction in viral fitness.
- COVID-19 variants causing reduction in vaccine efficacy or MAb treatments are primarily due to mutations on RBD (circled in blue) should not affect sensitivity to GRFT
- GRFT is a good candidate as a preventative agent against SARS-CoV-2 with a novel mechanism



Grant et al., *Scientific Reports,* 2020

GRFT Binding to Omicron Variant Spike Glycoprotein

- ITC comparing GRFT binding to SARS-CoV-2 Spike (Wuhan and Omicron)

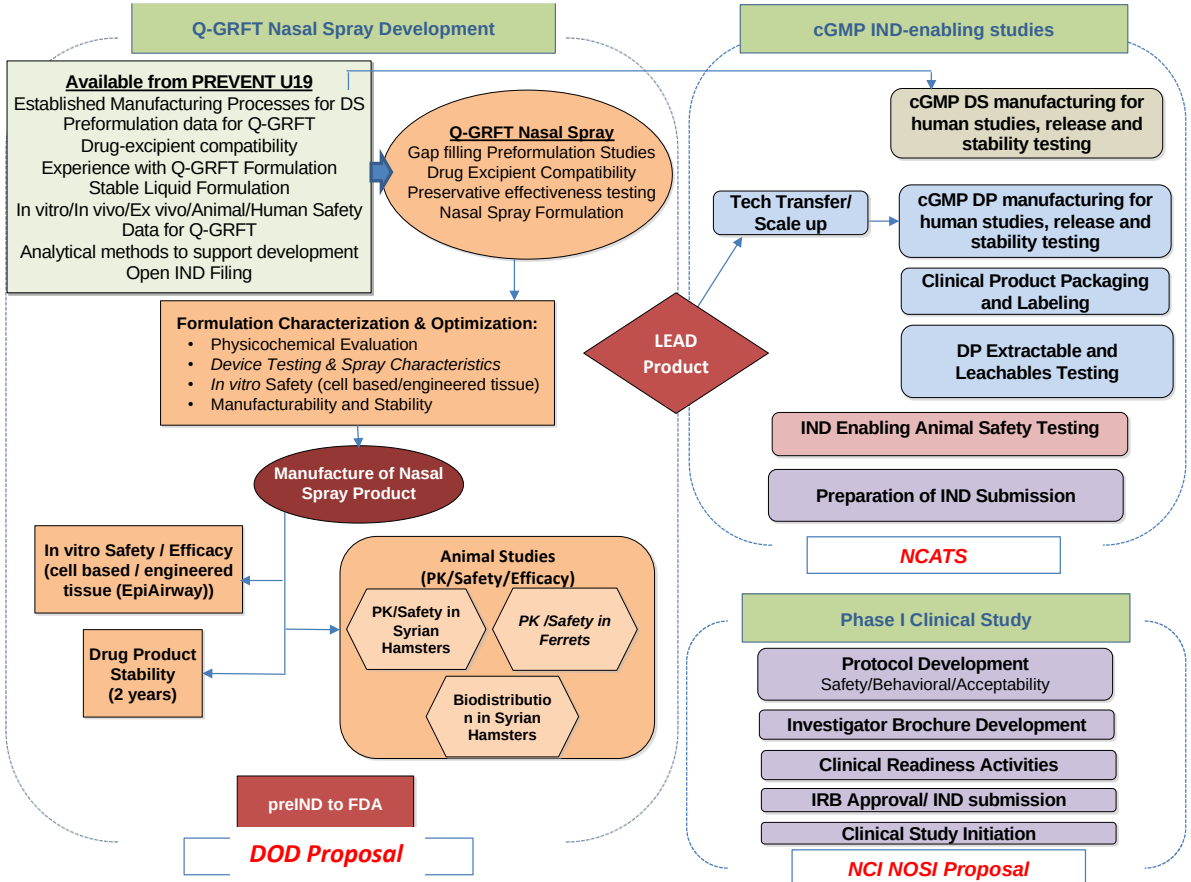


	Enthalpy, DH (kcal/mol)	Entropy, TDS (kcal/mol)	Free Energy, DG(kcal/mol)	Affinity, Kd(nM)	Stoichiometry (CVN:Spike)
GRFT into (Spike – Wuhan)	– 22.00 ± 0.22	– 11.53 ± 0.33	– 10.50 ± 0.33	28.7 ± 0.01	1.94 ± 0.40
GRFT into (Spike – Omicron)	– 20.90 ± 0.32	– 9.99 ± 0.32	– 10.90 ± 0.24	12.7 ± 0.01	2.91 ± 0.10

- GRFT affinity for Omicron Spike it twice that for Wuhan variant
- GRFT binds with a 3:1 stoichiometry to Omicron and a 2:1 stoichiometry to Wuhan

Q-GRFT COVID-19 Clinical Development: A Team Approach

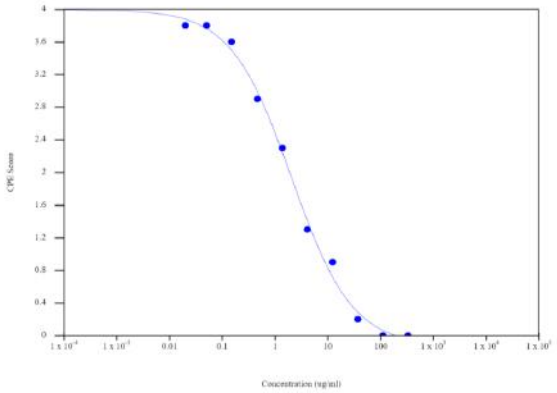
- Three agencies funded different aspects of the clinical development plan: NCI, DOD & NCATS
- Effort is a collaboration with Univ. Louisville and Univ. Pittsburgh
- 70g of GMP-certified Q-GRFT was available for clinical trial; additional 25g GLP Q-GRFT to complete pre-clinical studies.



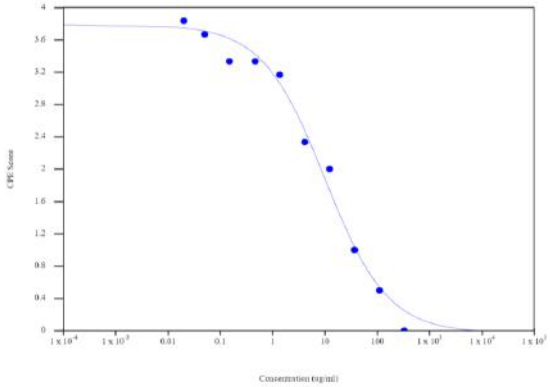
Q-GRFT Formulation was Important for Activity

- **Proper Q-GRFT intranasal formulation improved potency by 10-fold**

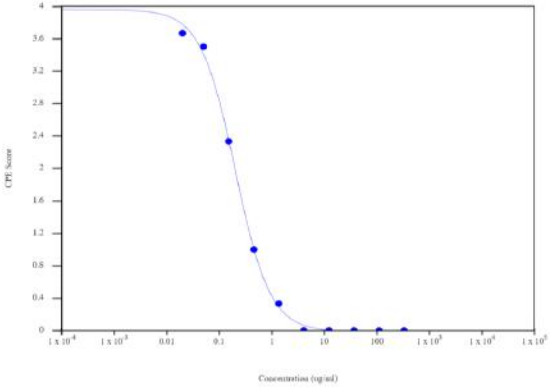
Q-GRFT
EC50=2.06 ug/ml



Formulation 3
EC50=10.07 ug/ml

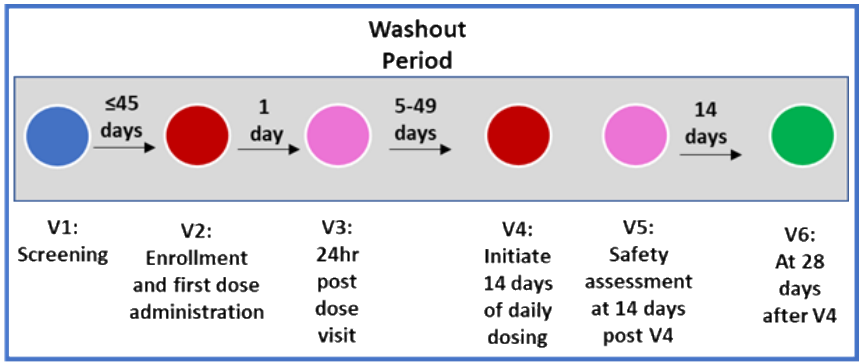


Formulation 20
EC50=0.21 ug/ml



Q-GRFT Clinical Development against SARS-CoV-2

- Initial clinical trials of Q-GRFT are *via* intranasal administration.
- For use in people with compromised immune systems or otherwise unvaccinated
- Trials will take place at the University of Pittsburgh and the University of Louisville
  - Phase 1a – single dose 1.5 mg/day (Univ. Louisville), successfully completed – no AE
  - Phase 1b – twice daily dosing (Q12), currently enrolling
  - Phase1b – 14 treatment days at 3.0 mg/day (Univ. Pittsburgh), currently enrolling



GRFT Summary and Future Efforts

- GRFT or Q-GRFT has successfully completed three Phase I clinical trials
- First intranasal Q-GRFT Phase I clinical trial for SARS-CoV-2 has been successfully completed
  - Q-GRFT approved to move to dose-escalation (3.0 & 6.0 mg/day)
  - Q-GRFT present in nasopharynx out to 24 hrs post administration
  - Evidence of *ex-vivo* efficacy
- Phase Ib clinical trials ongoing at Univ. Pittsburgh and Univ. Louisville
- Continued development of Q-GRFT fast-dissolving inserts, intravaginal rings and enemas for the prevention of HIV and other STDs

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Nina Darby
Shweta Ugaonkar

Centers for Disease Control

David Garber
Michael Lo

Funding

Get Involved in Natural Product Research at the NCI

Job opportunities in the Molecular Targets Program, NCI

- Stadtman Tenure Track Fellows:
  - Expertise in high-content cell-based screening for the discovery and mechanistic study of anticancer agents
  - Expertise in microbial fungal genetics, biochemistry and natural products
- Bioinformatics position with experience in biological and chemical data handling and analysis

Accepting applications August and September
Chemical Biology/Chemistry section of interest to natural product researchers.
For details see http://irp.nih.gov/
(under Careers/Trans-NIH Scientific Recruitments)

Or Email me at: okeefeba@mail.nih.gov