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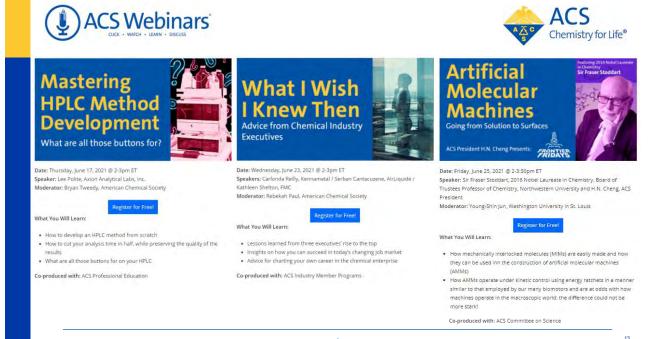


acsvoices.podbean.com/



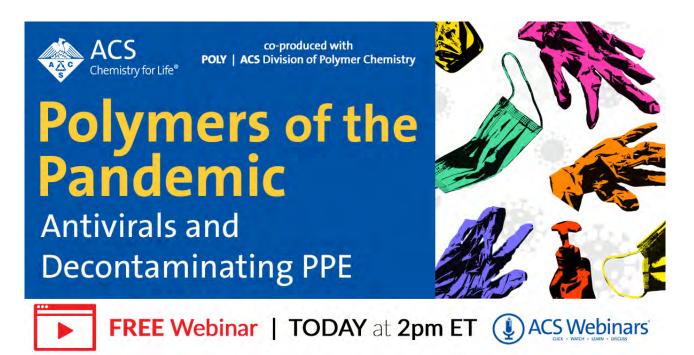
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Polymers of the Pandemic: Antivirals and Decontaminating PPE



Presentation slides are available now! The edited recording will be made available as soon as possible.

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 ${\it This ACS We binar is co-produced with the ACS Division of Polymer Chemistry.}$

Polymers of the Pandemic

Antivirals

Michael D. Schulz

Department of Chemistry, Macromolecules Innovation Institute, Center for Emerging, Zoonotic, and Arthropod-borne Pathogens, Virginia Tech Center for Drug Discovery Virginia Tech

mdschulz@vt.edu



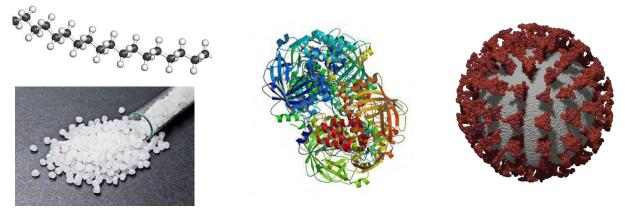




What is a polymer? What is a virus?

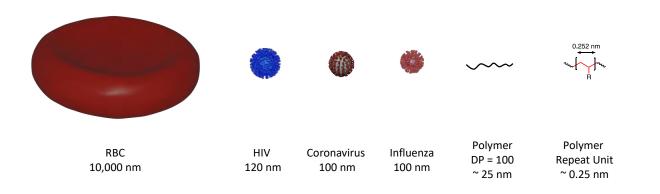
Polymer: A large molecule composed of many repeating units

Virus: A submicroscopic infectious agent that replicates only inside the living cells of an organism





How big is a polymer? How big is a virus?



NOT TO SCALE



Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

When were antiviral polymers discovered?

- 1930s
- 1940s
- 1950s
- 1960s
- 1970s



Antiviral Polymers: Early History

In the course of investigations concerned with problems relative to the pathogenesis of primary atypical pneumonia, a study was undertaken on the effects of inoculating mice with both a virus and a bacterium. The virus employed in these experiments is known as pneumonia virus of mice, and will hereafter be designated PVM. The bacterium used is a non-hemolytic streptococcus, designated streptococcus MG.

When the first experiments were carried out, it was considered that either of two possible results might develop; first, that streptococcus MG would have no discernible influence on the course of an infection induced by PVM; or second, that it might, by contributing to the establishment of a complex infection, cause the results to be more severe than those of infections induced by

PVM alone. Surprisingly, neither possibility evolved; instead, the inoculation of streptococcus MG in mice which previously had been inoculated with PVM resulted in a distinctly less severe infection.

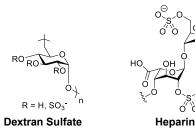


Antiviral Polymers: Early History

Subsequent studies in 1947 and 1948 directly tested various polysaccharides for antiviral activity against influenza and mumps. Some worked, others did not.

Green, R. H.; Woolley, D. W. *J. Exp. Med.* **1947**, *86*, 55-64. Ginsberg, H. S.; Goebel, W. F.; Horsfall, F. L. *J. Exp. Med.* **1948**, *87* (5), 385–410

Over a decade later, polyanionic character was recognized as key for antiviral activity.



Takemoto, K. K.; Liebhaber, H. *Virology* **1961**, *14* (4), 456 Takemoto, K. K.; Spicer, S. S. *Ann. N. Y. Acad. Sci.* **1965**, *130* (1), 365 Vaheri, A. *Acta Pathol. Microbiol. Scand.* **1964**, *60*, 1– 98



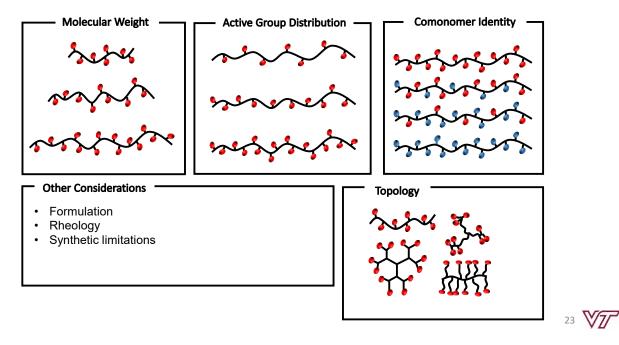
Antiviral Polymers: Early History

Polyanions continued to be developed

(especially in the context of anti-HIV materials)

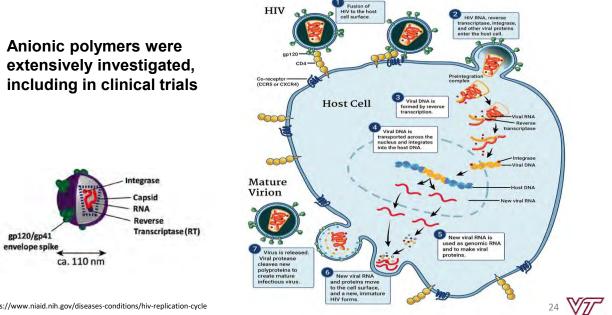
Polymers were developed as interferon inducers

Polynucleotides and oligonucleotides were developed both as interferon inducers and as antiviral agents that would bind to viral mRNA

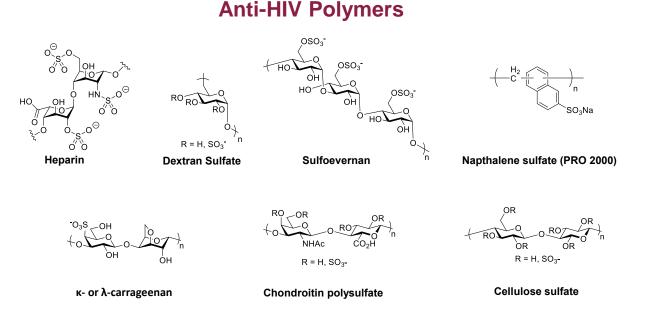


Polymer Parameters

Anionic Materials and Human Immunodeficiency Virus

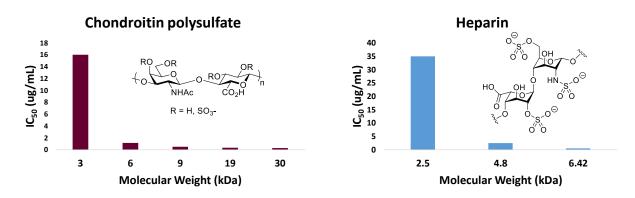


https://www.niaid.nih.gov/diseases-conditions/hiv-replication-cycle



Bianculli, R. H.; Mase, J. D.; Schulz, M. D. Macromolecules 2020, 53, 21, 9158

Anti-HIV Polymers: Effect of Molecular Weight

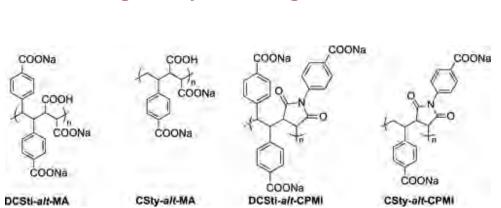


A polymer's molecular weight can be important in determining viral inhibition

- As molecular weight increases, the gains in antiviral potency begin to level off
- Polyvalency is a potential reason, though steric crowding of the virus may also play a role

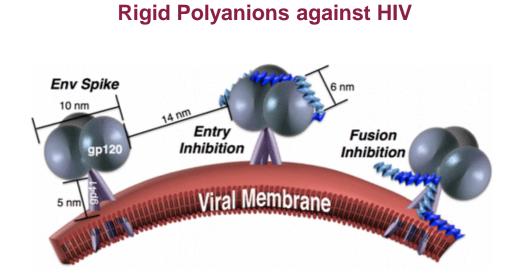
Jurkiewicz, E.; Panse, P.; Jentsch, K. D; Hartmann, H.; Hunsmann, G. *AIDS* **1989**, *3*(7), 423-427. Baba, M.; Declercq, E.; Schols, D.; Pauwels, R.; Snoeck, R.; Vanboeckel, C.; Vandedem, G.; Kraaijeveld, N.; Hobbelen, P.; Ottenheijm, H.; Denhollander, F. *J. Infect. Dis.* **1990**, *161* (2), 208-213.





Rigid Polyanions against HIV

Savage, A. M.; Li, Y.; Matolyak, L. E.; Doncel, G. F.; Turner, S. R.; Gandour, R. D. *J. Med. Chem.* **2014**, *57* (15), 6354–6363



Savage, A. M.; Li, Y.; Matolyak, L. E.; Doncel, G. F.; Turner, S. R.; Gandour, R. D. *J. Med. Chem.* **2014**, *57* (15), 6354–6363



Anti-HIV Polymers: Some Concluding Thoughts

Antiviral polymers targeting HIV have been more extensively studied than for any other viral disease

Clinical trials have faced considerable challenges: some polymers possess limited strain effectiveness, can enhance HIV infectivity, or can cause acute reactions in patients

Danial, M.; Klok, H.-A. Macromol. Biosci. 2015, 15, 9-35

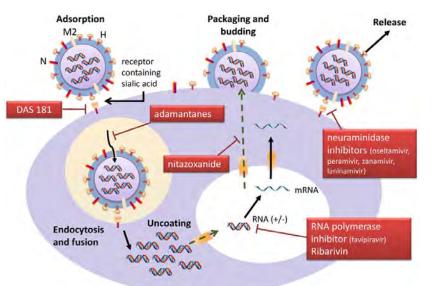
1918 Influenza: The Mother of All Pandemics

"An estimated one third of the world's population (or ≈500 million persons) were infected and had clinically apparent illnesses during the 1918–1919 influenza pandemic. The disease was exceptionally severe. Case-fatality rates were >2.5%, compared to <0.1% in other influenza pandemics. Total deaths were estimated at ≈50 million and were arguably as high as 100 million."



Taubenberger, J. K.; Morens, D. M. Emerg. Infect. Dis. 2006, 12, 15-22

30 17/



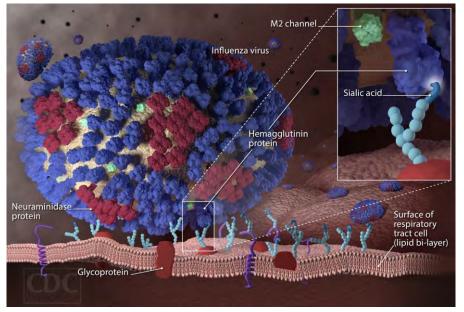
Influenza Virus



Li, T. C. M.; Chan, M. C. W.; Lee, N. Viruses 2015, 7(9), 4929-4944;

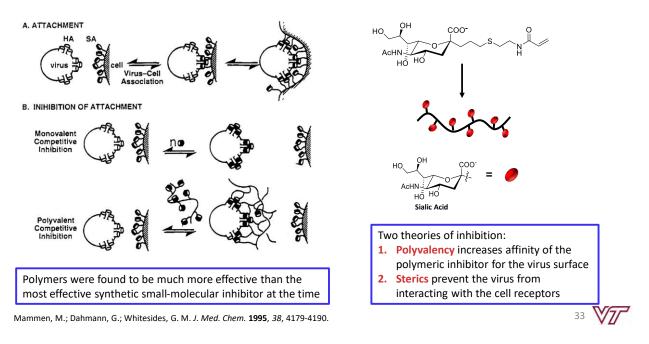


Influenza Infection



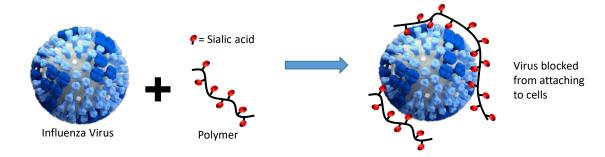
https://www.cdc.gov/flu/resource-center/freeresources/graphics/images.htm





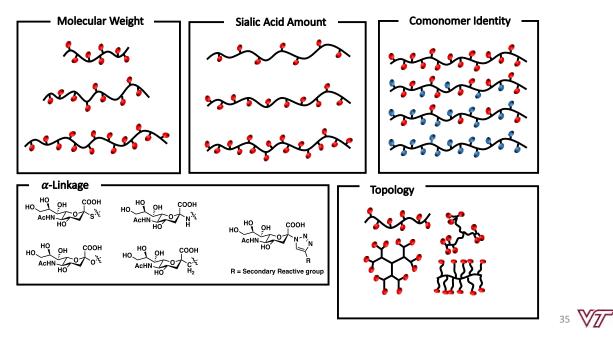
Polymeric Influenza Inhibitors

The Basic Concept: Polyvalency



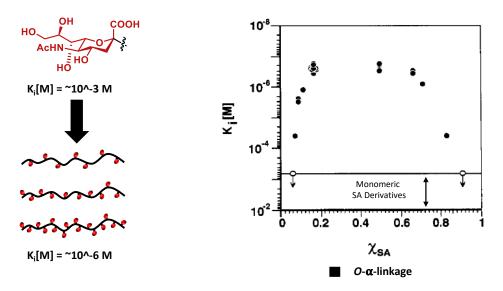
How do polymer parameters affect this interaction?





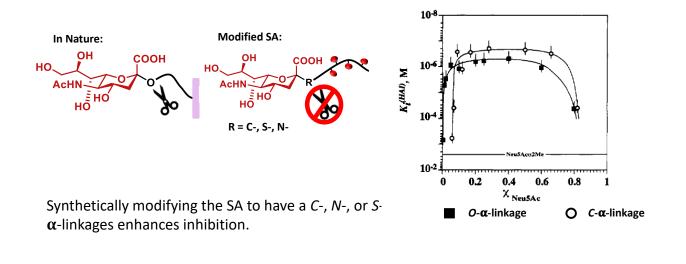
Anti-influenza Polymer Parameters

Sialic Acid Content



Spaltenstein, A.; Whitesides, G. M., J. Am. Chem. Soc. 1991, 113, 686-687.

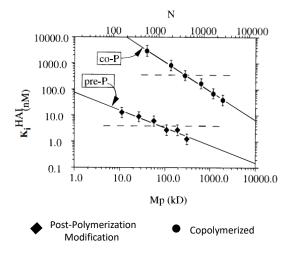




α-Linkage Identity and SA content

Sparks, M. A.; Williams, K. W.; Whitesides, G. M., J. Med. Chem. 1993, 36 (6), 778-783.

Molecular Weight and Polymerization Method

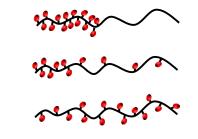


Increase in molecular weight enhances inhibition

• Upper limit of this effect has not been determined

J. Am. Chem. Soc. 1996, 118 (16), 3789-3800.

Copolymerization or Post Polymerization Modification?

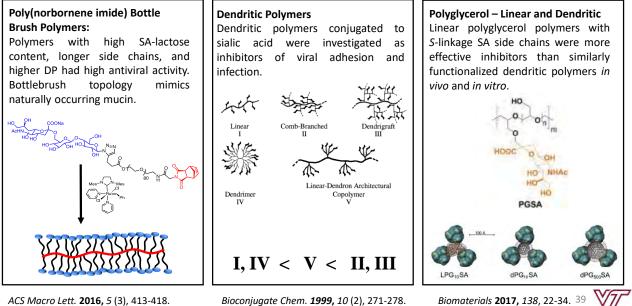


 Polymers produced by copolymerization of SAcontaining monomers were less effective than those synthesized by post-polymerization modification.

J. Med. Chem. 1995, 38 (21), 4179-4190. 38



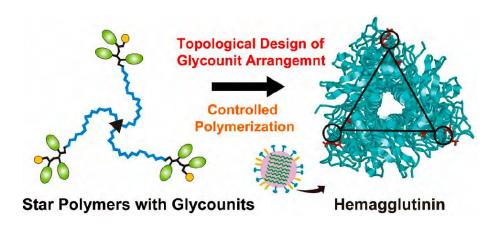
Topology and Backbone Identity



ACS Macro Lett. 2016, 5 (3), 413-418.

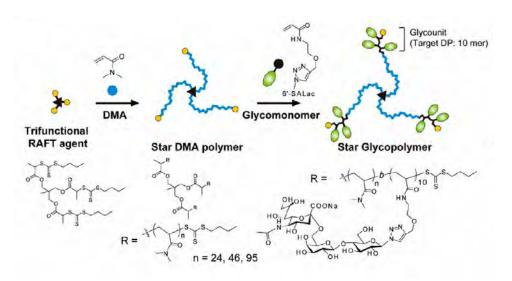
Bioconjugate Chem. 1999, 10 (2), 271-278.

Influenza: Targeting hemagglutinin



Nagao, M.; Matsubara, T.; Hoshino, Y.; Sato, T.; Miura, Y. Bioconjugate Chem. 2019, 30, 1192-1198



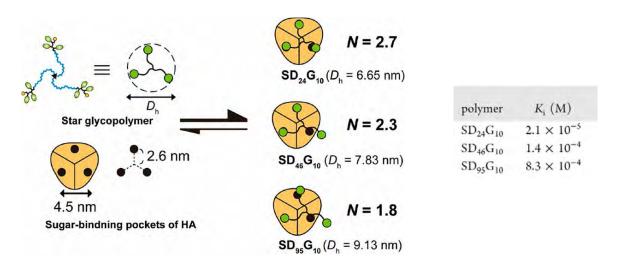


Influenza: Targeting hemagglutinin

Nagao, M.; Matsubara, T.; Hoshino, Y.; Sato, T.; Miura, Y. Bioconjugate Chem. 2019, 30, 1192-1198

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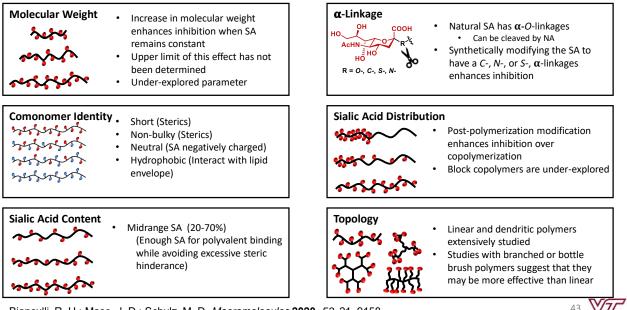
Influenza: Targeting hemagglutinin



Nagao, M.; Matsubara, T.; Hoshino, Y.; Sato, T.; Miura, Y. Bioconjugate Chem. 2019, 30, 1192-1198



Anti-influenza Polymer Parameters for Enhanced Inhibition



Bianculli, R. H.; Mase, J. D.; Schulz, M. D. Macromolecules 2020, 53, 21, 9158

In vivo studies

SA-functionalized polyacrylamide (DP~700, 10% SA content) was tested against mouse-adapted influenza virus.

Polymer was aerosolized and administered to mice by inhalation either 30 min before or 10 min after infection with the virus. Both groups had decreased mortality.

Subsequent studies produced similar results.

Gambaryan, A. S.; Boravleva, E. Y.; Matrosovich, T. Y.; Matrosovich, M. N.; Klenk, H. D.; Moiseeva, E. V.; Tuzikov, A. B.; Chinarev, A. A.; Pazynina, G. V.; Bovin, N. V. *Antiviral Res.* **2005**, *68* (3), 116–23



Influenza: Concluding Thoughts

While influenza vaccines are effective, they also have significant limitations

Antiviral polymers targeting influenza have shown promise, but key questions remain

45

Other Viruses

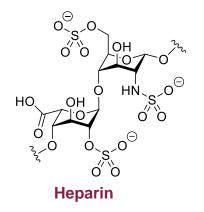
Herpes Simplex Virus Hepatitis Norovirus Respiratory syncytial virus Sendai virus Zika virus Ebola

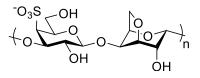
Antiviral polymers have been explored for each of these pathogens to some extent



COVID-19

Antiviral polymers are promising inhibitors of SARS-CoV-2





Carrageenan

Moakes, R. J. A.; Davies, S. P.; Stamataki, Z.; Grover, L. M. Adv. Mater. 2021, 2008304

Membrane

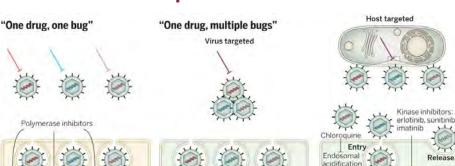
R

DEB025. SCY-635

Tandon, R.; Sharp, J. S.; Zhang, F.; Pomin, V. H.; Ashpole, N. M.; Mitra, D.; McCandless, M. G.; Jin, W.; Liu, H.; Sharma, P.; Linhardt, R. J.

J. Virol. 2021, 95, e01987. doi: 10.1128/jvi.01987-20



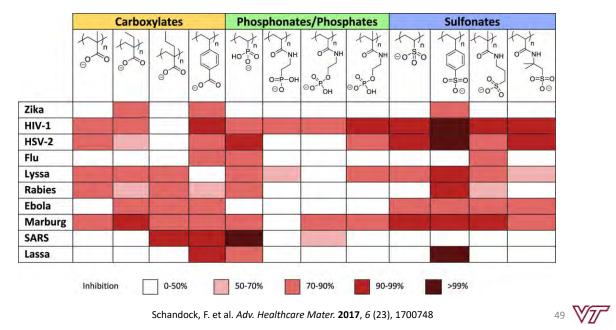


Broad-Spectrum Antivirals

Bekerman, E.; Einav, S. Science 2015, 348, 282-283



trafficking Fusion Genome replication Assembly Genome replication Genome Protein folding replication Gluco Translation sidase processing Lipid Other metabolism Protease inhibitors Polymerase inhibitors: BCX4430, T-705, CMX001 Interferon, Statins Celgosivin nitazoxanide



Broad-Spectrum Antiviral Polymers

Antiviral Polymers: Where do we go from here?

- COVID-19 will likely dominate the research landscape in this area for the foreseeable future
- Broad-spectrum antivirals are underdeveloped (a challenge for smallmolecule antiviral drugs as well)
- Common challenges in nanomedicine in general (biodegradability, metabolism, biodistribution, etc.) have received little attention in the context of antiviral polymers
- Assay development and refinement
- Potential applications in veterinary medicine, agriculture and other fields



Conclusions

Modern polymer synthesis techniques enable control over key polymer parameters

Antiviral polymers remain unexplored as approaches to treating most viral diseases

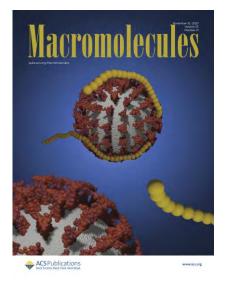
Cross-disciplinary collaboration is important

Opportunities abound

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For More Information

"Antiviral Polymers: Past Approaches and Future Possibilities" Bianculli, R. H.; Mase, J. D.; Schulz, M. D. *Macromolecules* **2020**, *53*, 21, 9158





Acknowledgments



Graduate Students: Brady Hall Ophelia Wadsworth Ryan Archer Tiffany Thompson Rachel Bianculli Hannan Almuzaini Jonathan Mase Nuran Iftekhar Megan Maza Connor Gallagher

Undergraduate Students:

Madison Bardot Elliot Shelton Will Vaughn Andy Brenner Agustin Fiorito Andrew Bigelow Samantha Scott Grace Dinges Alex Coley Piper MacNicol Javier Ortiz Alvarado



Center for Emerging, Zoonotic, and Arthropod-borne Pathogens

@SchulzLabVT



mdschulz@vt.edu









Polymers of the Pandemic: Detrimental Effects of Decontamination Methods on Polymers in Respirators

Emilie Rexeisen, PhD Product Engineering Specialist, 3M June 16, 2021

3M at a glance



- Sales in nearly every country
- \$32.1 billion in sales
- Four business groups
- 96,163 3Mers globally
- 122,416 patents
- 100+ straight years of dividends
- One of 30 companies on the Dow Jones Industrial Index

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Our four Business Groups

Safety & Industrial

Transportation & Electronics

Health Care

31



Consumer

56

3M Value Model

Vision

3M Technology Advancing Every Company 3M Products Enhancing Every Home 3M Innovation Improving Every Life

Strengths

- Manufacturing
- Global Capabilities
 Brand
- Dianc

Priorities

- 🍪 Portfolio
- Transformation
- Innovation
- HH People & Culture

Values

Inclusion Diversity Sustainability Respect, encourage, challenge

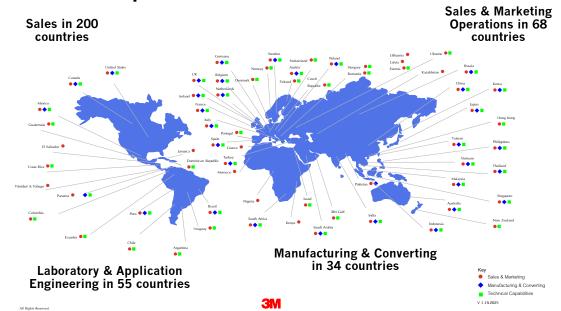
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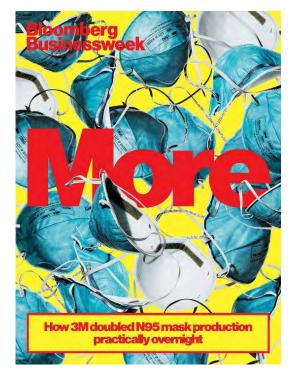
10 2021

3M

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2021 Global Capabilities





Challenge

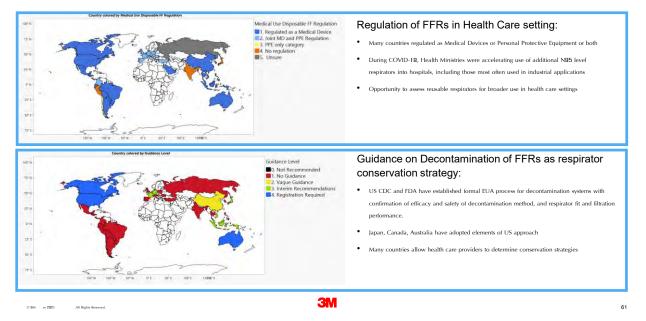
Unprecedented demand for PPE far exceeding supply for the entire industry

- Manufactured 2B+ respirators in 2020 more than tripling the volume in 2019 with goals to quadruple in 2021
- Producing over 95M respirators per month in US alone
- Plants running 24/7 making more respirators than ever before
- Resources from the entire corporation mobilized to scale-up new lines, qualify multiple raw material sources, commercialize new models, and meet all regional regulatory requirements
- Researched ways for hospitals to decontaminate, reuse, and extend the life of NB5 respirators
- Working with governments to break down trade barriers and direct respirators to serve areas of the world most in need
 - Launched a global effort to combat fraud and price gouging and help protect the public against those who try to exploit the unprecedented demand

ЗМ



Global Regulatory Landscape for FFRs and Decontamination



Can I decontaminate FFRs?

Per OSHA, decontamination of FFRs is only permissible for healthcare workplaces during certain crisis capacity circumstances.

As of April 2021, the US FDA has recommended workplaces to transition away from decontamination.

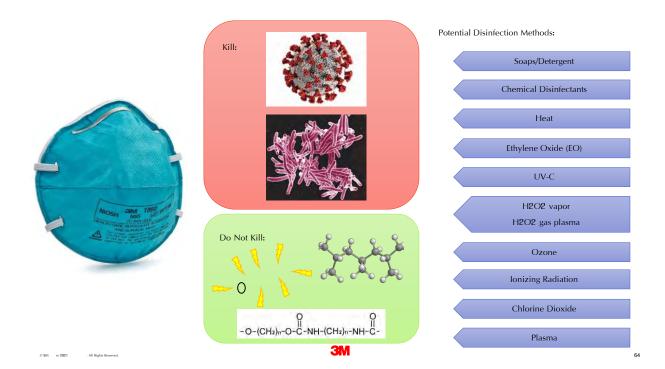
https://multimedia.3m.com/mws/media/18248680//decontamination-methods-for-3mn95-respirators-technical-bulletin.pdf

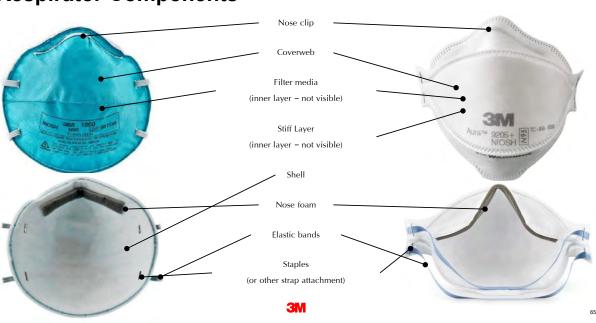
- 3M does not recommend decontaminating FFRs.
- Decontamination does not extend the service life of FFRs.



Evaluation of Decon Method Compatibility with 3M FFRs

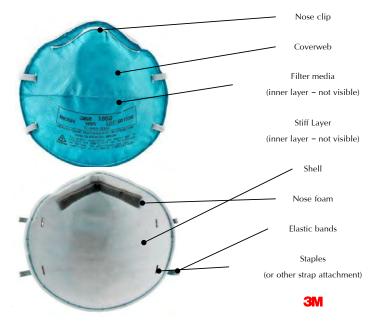
	Efficacy • Must inactivate target organism Safety • Must be safe for person wearing respirator	3M relied upon the decontamination method developer to confirm the germicidal efficacy of the method
MICH 1000 PM 1	Filtration Must not damage respirator's filtration 	If filtration is damaged or the respirator does not fit, it will
	Fit • Must not negatively affect respirator's ability to seal to the wear's face	not help reduce exposure to airborne particles at the level indicated
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Respirator Components

Respirator Components



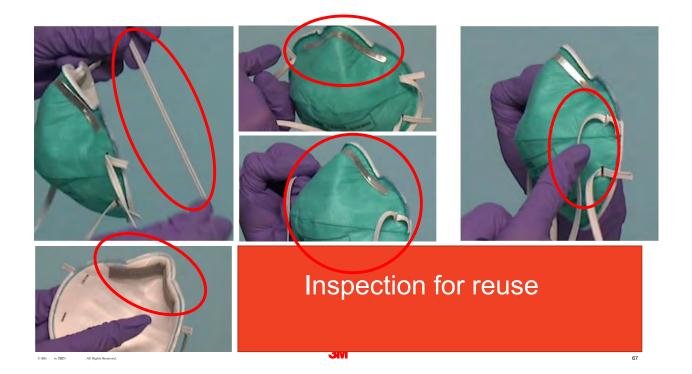
Impact on filter

Validation conducted using automated filter tester such as the TSI Automated Filter Tester 8130, used in generating filter data for meeting NIOSH standard 42 CFR part 84, Respiratory Protective Devices or European standard EN 148.

Impact on fit

Assessments are made of:

- nosefoam
- headbands
- cup condition



Audience Survey Question_

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

Which respirator component is adversely affected by heat?

- Noseclip
- Coverweb
- Filter media
- Shell
- Nosefoam



*3M is not assessing residuals or decontamination efficacy.

UV, VHP, Heat Methods

Method	Filter Media	Elastic	Nose foam	Shell	Residuals s	3 M Conclusions
UV-C		Can degrade at high high cycles				Maximum 100J/cm2 total exposure
VHP (if VHP is used in combination with another with another method, refer to both lines) both lines)					***	Straight VHP ok. VHP+plasma needs to be tested
Low Temp Moist Heat (85°C)			Can delaminate			Ok. Process flatfolds flat
Dry Heat (90-100°C)	Slightly Degrades filtration filtration efficacy		Can delaminate	Cup-style shrinks above 90°C above 90°C		Temperature control is important. Filtration efficiency decreases with Temperature*Time Temperature*Time
Microwave Generated Steam				Melting near metal components - creates holes creates holes		No Not well controlled
High Temp Steam (121°C)	Degrades filtration efficacy filtration efficacy		Becomes sticky, loses loses elasticity w/ multiple multiple cycles	Shrinks – will lead to leaks in to leaks in cup style style		Only for Aura or VElex-styles, only 1 cycle

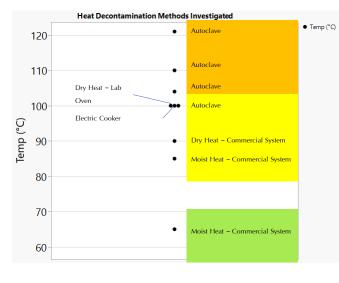
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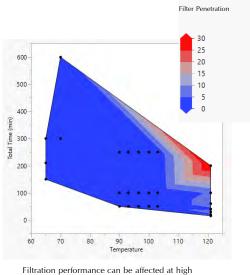
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Heat Decontamination Methods





temperatures, especially at long exposure times.

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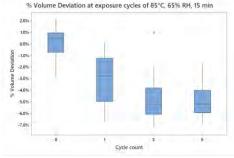
69

% Deviation from Initial

High temperatures cause shrinkage of shell.



At high temperatures, the respirator shrinks considerably, which compromises fit.

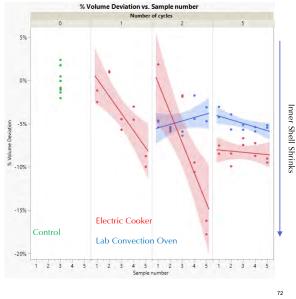


Even at moderate temperatures, a 5% shell shrinkage can be observed.

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Electric Cooker provides inconsistent temperature profile, which leads to shell shrinkage.





Effect of 121°C of PU foam

Control



 $2 \, \mathrm{cycles}$



10 cycles



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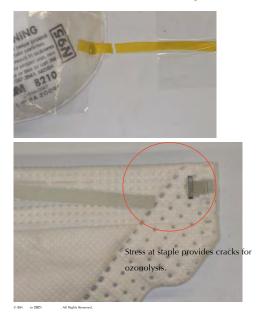
*3M is not assessing residuals or decontamination efficacy

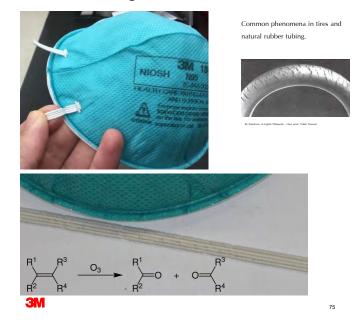
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Other Chemical & Radiation Methods

Method	Filter Media	Elastic	Nose foam	Shell	Residuals	3M Conclusions
Ozone		Loses elasticity after 1 cycle	Loses elasticity after 1 cycle		***	No
Chlorine dioxide		Loses elasticity after multiple cycles	Loses elasticity after multiple cycles		***	Residuals unknown. Low cycle counts (≦II)
Plasma (chemical dependent)	Can degrade filtration efficacy	Can affect if creating ozone	Can affect if creating ozone			Test each individually
lonizing Radiation (gamma, e-beam, X-ray)	Degrades filtration efficacy					No
Isopropanol	Degrades filtration efficacy filtration efficacy					No
Supercritical CO2	Degrades filtration efficacy filtration efficacy			Cup-style shrinks		No
Soaps/Detergent	Degrades filtration efficacy filtration efficacy					No
Quat solution	Degrades filtration efficacy filtration efficacy				***	No
Ethylene Oxide	N/A	N/A			***	No

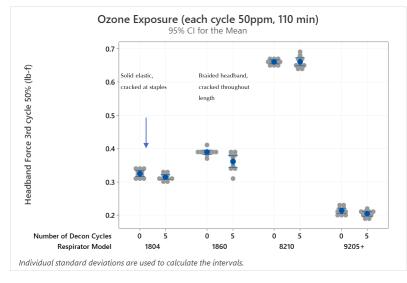
Rubbers are susceptible to ozone cracking.





Changes in elastic band force with exposure to ozone.





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Ozone degradation of nosefoam



Nosefoam after 1 cycle loses ability to recover to full thickness, which compromises fit performance.

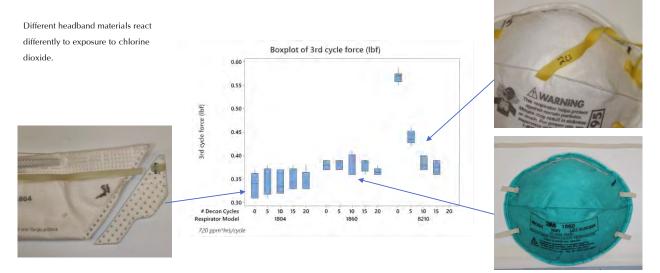


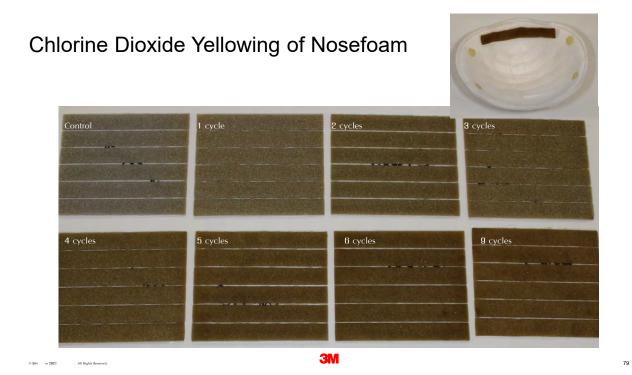
After multiple cycles, nosefoam degrades completely.

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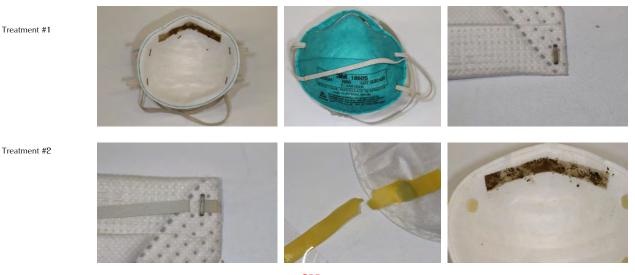
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Chlorine Dioxide Decontamination





Plasma exposure effects are dependent upon chemical species created.

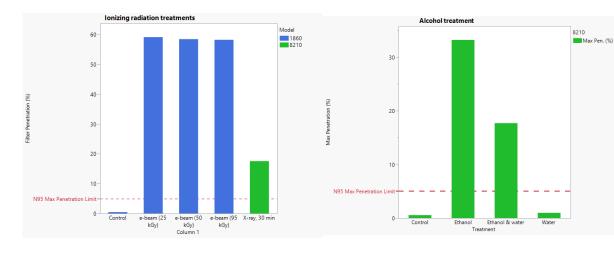


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Ionizing radiation and chemical disinfectants destroy electrostatic filtration.



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Pandemic Lessons Learned

3M is sharing expertise on how to better prepare for future pandemics and emergencies with governments, customers, and stakeholders around the world.

- 3M rose to the challenge of COVID-19 drawing from our years of experience responding to other global challenges.
- COVID-19 has been a test of national preparedness plans and demonstrated how supply chains, governments, and health care systems can be stretched beyond their limits by the unexpected.
- 3M proudly partnered with governments around the world to expand NB5 and other respirator production capacity including in North America, Europe and Asia to help those regions respond to the pandemic and build resiliency to face global challenges.





Polymers of the Pandemic

Antivirals and Decontaminating PPE



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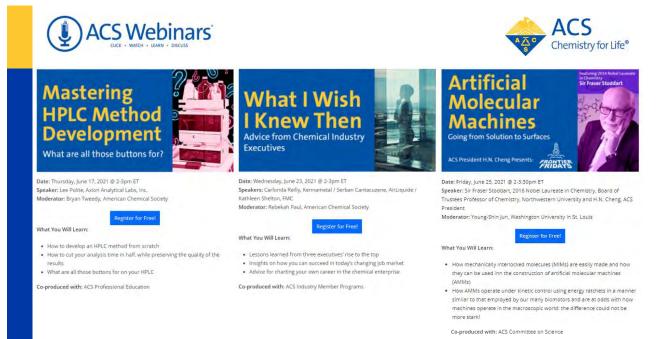
Polymers of the Pandemic: Antivirals and Decontaminating PPE



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