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Polymers of the Pandemic: Antivirals and Decontaminating PPE

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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?

- **RBC:** 10,000 nm
- **HIV:** 120 nm
- **Coronavirus:** 100 nm
- **Influenza:** 100 nm
- **Polymer DP = 100:** ~ 25 nm
- **Polymer Repeat Unit:** ~ 0.25 nm

*NOT TO SCALE*
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.


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

Takemoto, K. K.; Liebhaber H. Virology 1961, 14 (4), 456

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

- Molecular Weight
- Active Group Distribution
- Comonomer Identity

Other Considerations
- Formulation
- Rheology
- Synthetic limitations

Anionic Materials and Human Immunodeficiency Virus

Anionic polymers were extensively investigated, including in clinical trials

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

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

Rigid Polyanions against HIV

Savage, A. M.; Li, Y.; Matolyak, L. E.; Doncel, G. F.; Turner, S. R.; Gandour, R. D.

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Rigid Polyanions against HIV

Savage, A. M.; Li, Y.; Matolyak, L. E.; Doncel, G. F.; Turner, S. R.; Gandour, R. D.
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


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.”

Influenza Virus

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

Influenza Infection

Polymeric Influenza Inhibitors

Polymers were found to be much more effective than the most effective synthetic small-molecular inhibitor at the time.


Two theories of inhibition:
1. **Polyvalency** increases affinity of the polymeric inhibitor for the virus surface
2. **Sterics** prevent the virus from interacting with the cell receptors

The Basic Concept: Polyvalency

How do polymer parameters affect this interaction?
Anti-influenza Polymer Parameters

Molecular Weight

Sialic Acid Amount

Comonomer Identity

α-Linkage

Topology

Sialic Acid Content

$K_i[M] = \sim 10^{-3} \text{ M}$

$K_i[M] = \sim 10^{-6} \text{ M}$

**α-Linkage Identity and SA content**

Synthetically modifying the SA to have a C-, N-, or S-α-linkages enhances inhibition.


---

**Molecular Weight and Polymerization Method**

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


Topography and Backbone Identity

**Poly(norbornene imide) Bottle Brush Polymers:**
Polymers with high SA-lactose content, longer side chains, and higher DP had high antiviral activity. Bottlebrush topology mimics naturally occurring mucin.

**Dendritic Polymers**
Dendritic polymers conjugated to sialic acid were investigated as inhibitors of viral adhesion and infection.

**Polyglycerol – Linear and Dendritic**
Linear polyglycerol polymers with S-linkage SA side chains were more effective inhibitors than similarly functionalized dendritic polymers *in vivo* and *in vitro*.

\[ \text{I, IV < V < II, III} \]

---

**Influenza: Targeting hemagglutinin**

**Star Polymers with Glycounits**

**Topological Design of Glycounit Arrangement**

**Controlled Polymerization**

---


Influenza: Targeting hemagglutinin

Anti-influenza Polymer Parameters for Enhanced Inhibition

**Molecular Weight**
- Increase in molecular weight enhances inhibition when SA remains constant
- Upper limit of this effect has not been determined
- Under-explored parameter

**Comonomer Identity**
- Short (Sterics)
- Non-bulky (Sterics)
- Neutral (SA negatively charged)
- Hydrophobic (Interact with lipid envelope)

**Sialic Acid Content**
- Midrange SA (20-70%)
  (Enough SA for polyvalent binding while avoiding excessive steric hinderance)

**α-Linkage**
- Natural SA has α-O-linkages
  - Can be cleaved by NA
  - Synthetically modifying the SA to have a τ-C, N, or S, α-linkages enhances inhibition

**Sialic Acid Distribution**
- Post-polymerization modification enhances inhibition over copolymerization
  - Block copolymers are under-explored

**Topology**
- Linear and dendritic polymers extensively studied
  - Studies with branched or bottle brush polymers suggest that they may be more effective than linear

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.


Influenza: Concluding Thoughts

While influenza vaccines are effective, they also have significant limitations.

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

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

Heparin

Carrageenan

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.


Broad-Spectrum Antivirals

“One drug, one bug”
“One drug, multiple bugs”

Host targeted

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

For More Information

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

Our four Business Groups

Safety & Industrial  Transportation & Electronics  Health Care  Consumer
3M Value Model

Strengths
- Technology
- Manufacturing
- Global Capabilities
- Brand

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

Priorities
- Portfolio
- Transformation
- Innovation
- People & Culture

Values
- Inclusion
- Diversity
- Sustainability
- Respect, encourage, challenge

2021 Global Capabilities

Sales in 200 countries

Laboratory & Application Engineering in 55 countries

Sales & Marketing Operations in 68 countries

Manufacturing & Converting in 34 countries

Key:
- Sales & Marketing
- Manufacturing & Converting
- Technical Capabilities

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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 N95 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
Global Regulatory Landscape for FFRs and Decontamination

Regulation of FFRs in Health Care setting:
- Many countries regulated as Medical Devices or Personal Protective Equipment or both
- During COVID-19, Health Ministries were accelerating use of additional N95 level respirators into hospitals, including those most often used in industrial applications
- Opportunity to assess reusable respirators for broader use in health care settings

Guidance on Decontamination of FFRs as respirator conservation strategy:
- US CDC and FDA have established formal EUA process for decontamination systems with confirmation of efficacy and safety of decontamination method, and respirator fit and filtration performance.
- Japan, Canada, Australia have adopted elements of US approach
- Many countries allow health care providers to determine conservation strategies

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/1824869O/decontamination-methods-for-3m-n95-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

Filtration
- Must not damage respirator’s filtration

Fit
- Must not negatively affect respirator’s ability to seal to the wearer’s face

If filtration is damaged or the respirator does not fit, it will not help reduce exposure to airborne particles at the level indicated.

3M relied upon the decontamination method developer to confirm the germicidal efficacy of the method.

Potential Disinfection Methods:

- Soaps/Detergent
- Chemical Disinfectants
- Heat
- Ethylene Oxide (EO)
- UV-C
- H2O2 vapor
- H2O2 gas plasma
- Ozone
- Ionizing Radiation
- Chlorine Dioxide
- Plasma

Kill:

Do Not Kill:
Respirator Components

- Nose clip
- Coverweb
- Filter media
  (inner layer – not visible)
- Stiff Layer
  (inner layer – not visible)
- Shell
- Nose foam
- Elastic bands
- Staples
  (or other strap attachment)

Impact on filter
Validation conducted using automated filter tester such as the TSI Automated Filter Tester (AFT), used in generating filter data for meeting NIOSH standard 42 CFR part 84, Respiratory Protective Devices or European standard EN 149.

Impact on fit
Assessments are made of:
- nose foam
- headbands
- cup condition
Inspection for reuse

**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
UV, VHP, Heat Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Filter Media</th>
<th>Elastic</th>
<th>Nose foam</th>
<th>Shell</th>
<th>Residuals</th>
<th>3M Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>UV-C</td>
<td>Can degrade at high high cycles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Maximum 100J/cm² total exposure</td>
</tr>
<tr>
<td>VHP (if VHP is used in combination with another with another method, refer to both line both lines)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Straight VHP ok. VHP/PFPA needs to be tested</td>
</tr>
<tr>
<td>Low Temp Moist Heat (65°C)</td>
<td>Can delaminate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ok. Process Flatfolds Flat</td>
</tr>
<tr>
<td>Dry Heat (85-105°C)</td>
<td>High temp degradation filter efficiency</td>
<td>Can delaminate</td>
<td>Cap-style filters above 85°C about 85°C</td>
<td></td>
<td></td>
<td>Temperature control is important. Filtration efficiency decreases with Temperature x Time Temperature x Time</td>
</tr>
<tr>
<td>Microwave Generated Steam</td>
<td></td>
<td>Cooking, not melt components — create yellow orange stains</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Temp Steam (121°C)</td>
<td>High temp degradation filter efficiency</td>
<td>Becomes sticky, loses elasticity at multiple multiple cycles</td>
<td></td>
<td></td>
<td></td>
<td>Only for Aura or VFlex-styles, only 1 cycle</td>
</tr>
</tbody>
</table>

*3M is not assessing residuals or decontamination efficacy.

Heat Decontamination Methods

Filtration performance can be affected at high temperatures, especially at long exposure times.
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.

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

Temperature varied significantly throughout the stack.
## Effect of 121°C of PU foam

### Control

![Image of Control]

### 2 cycles

![Image of 2 cycles]

### 10 cycles

![Image of 10 cycles]

## Other Chemical & Radiation Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Filter Media</th>
<th>Elastic</th>
<th>Nose foam</th>
<th>Shell</th>
<th>Residuals</th>
<th>3M Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorine</td>
<td></td>
<td></td>
<td>Loses elasticity after 1 cycle</td>
<td></td>
<td></td>
<td>***</td>
</tr>
<tr>
<td>Chlorine dioxide</td>
<td></td>
<td></td>
<td>Loses elasticity after multiple cycles</td>
<td></td>
<td></td>
<td>***</td>
</tr>
<tr>
<td>Plasma (chemical dependent)</td>
<td>Can degrade filtration efficacy</td>
<td>Can affect if creating ozone</td>
<td>Can affect if creating ozone</td>
<td></td>
<td>***</td>
<td>Test each individually</td>
</tr>
<tr>
<td>Ionizing Radiation (gamma, e-beam, X-ray)</td>
<td>Degrades filtration efficacy</td>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Isopropanol</td>
<td></td>
<td></td>
<td>Degrades filtration efficacy</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Ethylene Oxide</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
<td>***</td>
<td>No</td>
</tr>
</tbody>
</table>

*3M is not assessing residuals or decontamination efficacy.
Rubbers are susceptible to ozone cracking.

Changes in elastic band force with exposure to ozone.
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.

Chlorine Dioxide Decontamination

Different headband materials react differently to exposure to chlorine dioxide.

Boxplot of 3rd cycle force (lbf)
Chlorine Dioxide Yellowing of Nosefoam

Plasma exposure effects are dependent upon chemical species created.
Ionizing radiation and chemical disinfectants destroy electrostatic filtration.

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 N95 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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