The Coronavirus Pandemic: What are the Options?

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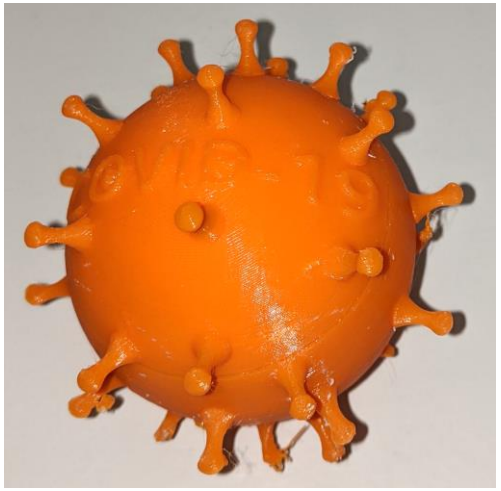

About Nanotech Plus, LLC

- Alliance of Consultants established in 2004
- We provide the team matched to the project. www.nanotechplus.net, www.nano-biz.com, www.consolidatednanotech.com
- We specialize in solving the challenges of commercializing advanced materials
- Focus areas: Pharmaceuticals, Energy Generation and Storage, Coatings, Composites, and more
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Outline of the Talk

1) Setting the Stage: How bad is the current pandemic?
2) About the Disease:

    Contagion, Types, Time Course, Treatments
3) Description of the Coronavirus
4) What can be done to change the pandemic's course?
5) Diagnostic Needs and Development
6) Vaccine Challenges
7) Antiviral Development
8) Q+A

Setting the Stage: How Bad is it?

Some Current Viral Epidemics

- Examples: Coronaviruses (SARS, MERS), Zika, AIDS, Dengue, Polio, Influenza, Mononucleosis, Herpes, Norovirus, Hepatitis, Ebola, Measles, etc.

Some Current Bacterial Epidemics

- Examples: E. Coli, Brucella (unpasteurized dairy), Listeria, Legionella, Gonorrhea, etc.

How Contagious is COVID-19?

Virus	**R0** (number of additional people infected from 1 infected individual)
• COVID-19	2.0-3.3
• SARS	3.0
• MERS	2-5
• Ebola	2
• Measles	12-18
• Influenza	1.7-1.8 in 2009 H1N1 in US
• Zika	1.8-5.8

Types of COVI-19 Infections

- Asymptomatic
- Mild Upper Respiratory Infection – similar to a cold
- Common – some lung involvement
- Severe – respiratory distress
- Multi-organ involvement – ICU
  Can involve heart, kidney, and even lead to gangrene
  60-70% of cases in the ICU die (Wuhan)
- Asymptomatic – common
  make up ~80% of cases

Course of Infection

- From the mild to common cases:

  1) Viremia: 0 -10 days

  2) Acute: pneumonia 7-10 days to 14 days
  - viral production peaks

  3) Recovery: 14-21 days
- This is a longer course than SARS/MERS
- For severe cases – at 1-2 weeks

  Need to get virus production under control

Treatments: Current Anti Viral Usage

- In China, the following antivirals have been tried:
  1) Lopinavir/Ritonavir – no clear benefit in severe cases
  2) Remdesivir – no information as of 3/27/2020
  3) Interferon – not shown to be effective
  4) Chloroquine/hydroxychloroquine-positive results are unproven
  5) Azithromycin
- Only used in early stages of disease.
- In NYC – often using chloroquine/hydroxychloroquine/ azithromycin – few side effects, but not very effective

Mechanisms of Mortality

- Coinfection ~ → pneumonia ~ ½ the fatal cases
- Viral damage to lungs or other organs- especially heart!

  1) 20% of patients had myocardial damage – up to 50% mortality

  2) Patients with underlying cardiovascular conditions have higher mortality, but even previously healthy individuals have ~20% mortality

- Overly aggressive immune response ~ 20%
  Can be failure to control viremia or cytokine storm, i.e. low levels of virus present
- Myocardial damage can be direct viral infection or immune response

Treatments: Anti Inflammatories

- If the person survives the coronavirus- then immune responses are similar to influenza infections
- Even If coronavirus viral production continues declines after 1-2 weeks, immune system responses can be fatal – not directly from virus!
- Therapies for severe cases:
  1) Steroids- highly debated!
  2) Very high doses (2 grams) iG – can be used in earlier stages
  3) Anti- IL-6 Tocilizumab- efficacy hard to evaluate.
  4) Other immune suppressors

Other treatments: anti coagulants- up to 2 weeks. New pulmonary anti-inflammatory: Immunomet 156 being evaluated.

- Summary: some immune suppression and anti coagulants can be life saving!

About Coronaviruses

- Coronaviruses are the largest RNA viruses at 125 nm 7 infect humans
- SARS Co V2 – 30kb. 20 kb – non-structural, 10 kb structural and accessory proteins. 80% homology with SARS-CoV1, 96% with some bat coronaviruses
- Enveloped and has 4 proteins: S (spike), E (envelope), M (membrane), N (nucleocapsid)
- Structural proteins not conserved!

Mechanism of SARS CoV2

- SARS CoV1 and SARS CoV2 use the ACE2 pathway to gain entry into the cell
- Angiotensin – Converting-Enzyme 2 (ACE2) primarily is involved in maturing angiotensin- important in controlling blood pressure and other functions
- ACE2 is expressed in heart, lungs, kidney and intestines
- CoV2 uses the spike protein (S) to gain entry
- S1 binds to the ACE2 site, S2 does membrane fusion
- Note that MERS uses a different mechanism to enter cells

How do we change the course of the Pandemic?

Passive Measures

1) Track cases/contacts.
2) Diagnostics:
   A) Direct virus detection
   Large testing labs gearing up
   B) Detection of antibodies
   POC tests could be available in less than 2 months
3) Isolation/Social Distancing
4) Protective Equipment

Active Measures

1) Better Models!
2) Vaccines
3) Antivirals

Diagnostic Needs: Detection

- Detection Methods:

  Direct viral detection (PCR)

  Indirect detection: Antibodies
- Direct detection allows determination of infected individuals and viral loads
  Highly accurate – but time consuming
- Indirect detection shows who is currently infected or has survived and is now immune
  Less accurate, faster, can be POC- BD/Biomedomics
- In competition with WHO, CDC developed direct detection kits – but were not accurate

Better Models Needed!

In Vivo

- Challenges: virus replicates in numerous animal models, but fails to cause disease even in non-human primates
- Can cause sneezing in ferrets
- Humanized mouse model developed for SARS/MERS Scaleup underway- Jackson Labs in several weeks

In Vitro

- Wyss Institute Lab on a Chip – being commercialized by Emulate, Inc
- Lung model has been used in influenza – but not ready for COVID-19

Vaccine Development

Good News: Lots of Companies Trying New Technology
(Selected companies)

- Adenovirus: Altimmune, J+J, Vaxart
- Nucleotide: Arcturus, BioNTech, Curevac, Inovio, LinearRX, Moderna, Zydus Cadila
- Protein: Generix, Heat Biologics, Vaxil Biotherapeutics
- Recombinant/Attenuated: Clover/GSK, Codagenix, Novavax, Sanofi, Tonix, Vaxart
- VLP: Geovax, iBio, Medicago, Novavax

Bad News

- Vaccine development is typically 5 years or more
- Vaccines can be harmful!

  a) Antibody Dependent Enhancement (ADE) and

  b) Th2 immunopathology
- Only Sanofi of the "Big 4" vaccine manufacturers has mounted a COVID-19 specific effort- others choosing to partner instead

Antiviral Development

RNAi

- Vir Biotechnologies: very well funded
  Partnered with Alnylam
  GSK recently funded with $250M
  Challenges: few successful RNAi drugs in market – delivery systems are challenging
- Sirnaomics

Viral Blockers

- Apeiron: protein-based technology
  – In clinical trials in China
- Nanoviricides: ligands mimicking binding site bound to a soft polymer
  – Developed MERS ligands prior

Antiviral Development, Cont'd

mAb

- Abcellera – partnered with Lilly
  Developed 500 mAb from one patient
- Beijing Defengrei – in clinical trials
  Targeting Factor 5A
- InflaRx – targeting Factor 5A
- Harbor Biomed – partnered with Mt. Sinai
  Targeting Spike protein
- ImmunoPrecise Antibodies – partnered with EVQLV, Ligand Pharmaceuticals

Other

- Pharmamar – natural product from tunicates targeting elongation factor 1-A

Q+A

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