

27th ECCMID, Vienna, Austria

**Important Highlights in  
Basic Virology:  
*Deep Sequencing and Viral Discovery***

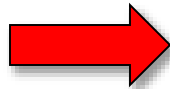
• **Lynn Enquist**



**PRINCETON  
UNIVERSITY**



## The general forces driving modern virology

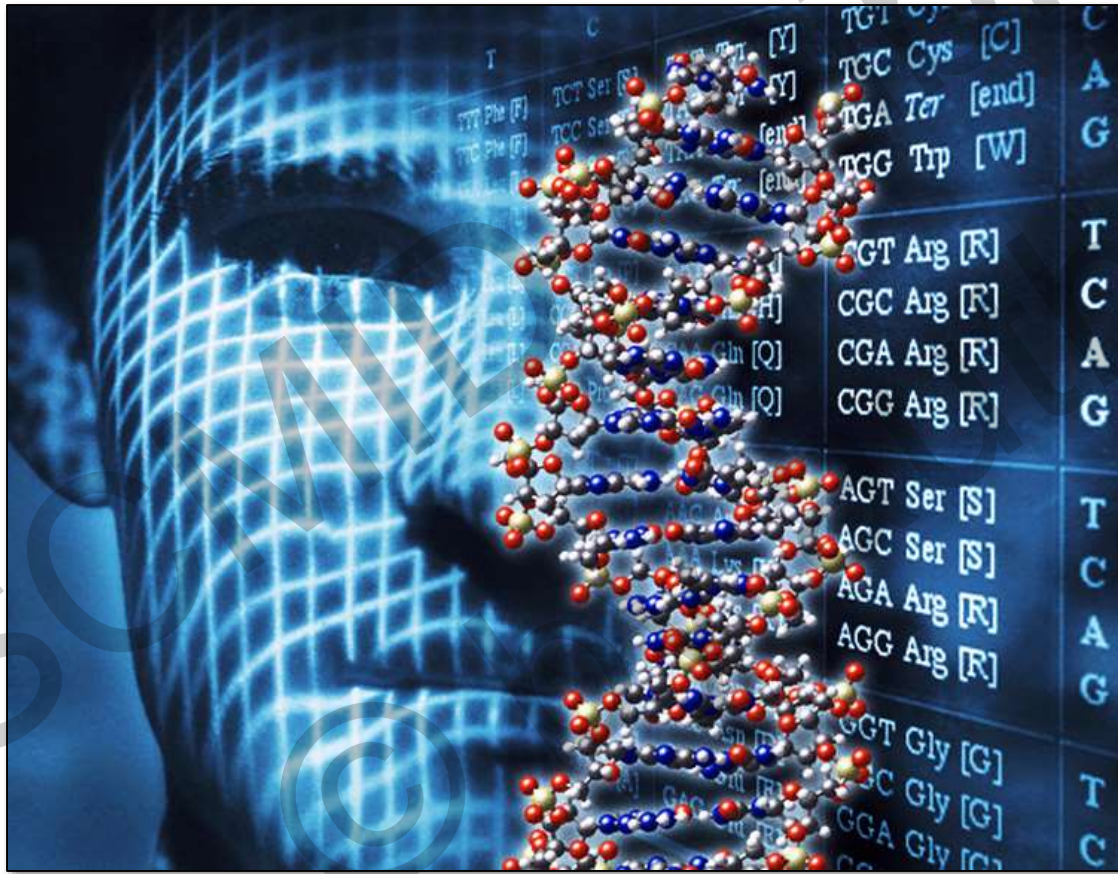


- Technology development,
- Vast amounts of information,
- Public health needs,
- Public perceptions,
- Personal curiosity.

**Next generation sequencing** – powerful machines to sequence DNA & RNA rapidly (hours)

**Deep sequencing** – aiming for a higher number of replicate reads of each region of a sequence; deep coverage=millions of base reads

**New technology with massive data accumulation and analysis is changing virology fundamental research**



## **Virus discovery – a whole new world thanks to next generation nucleic acid sequencing!**

We used to be able to identify and study only the viruses we could grow in the lab

Often we had no animal model for infection.

Recently, there has been a revolution in virus discovery. We literally can know every viral genome in almost any environment. We don't need to be able to grow anything.

This may be my most favorite paper of 2016.

**Mang. S. et al, 2016, Redefining the invertebrate RNA virosphere, *Nature***

A groundbreaking study of the RNA virosphere of the most populous animals - those without backbones such as insects, spiders and worms and that live around our houses.

## **Pioneering study of invertebrate virome discovers 1,445 viruses with RNA genomes, including several new families**

Authors sequenced the transcriptomes of over 220 invertebrate species sampled across nine animal phyla.

The identified viruses fill major gaps in the RNA virus phylogeny and reveal an evolutionary history that is characterized by both host switching and co-divergence.

Together, these data present a view of the RNA virosphere that is more phylogenetically and genomically diverse than that depicted in current classification schemes and provide a more solid foundation for studies in virus ecology and evolution.

**Obviously, we have only scratched the surface of the world of viruses –what are they doing out there and are they a source of new human infections?**

## **Sequencing: an amazing technology for virus discovery;** - so many new approaches – here are two of them

**McCrone, JT, Lauring AS. 2016. Measurements of intrahost viral diversity are extremely sensitive to systematic errors in variant calling. *J. Virol.***

Advances in sequencing technology have made it feasible to sequence patient-derived viral samples at a level sufficient for detection of rare mutations. The authors found that the accuracy of previously benchmarked analysis pipelines was greatly reduced under patient-derived conditions.

Application of their modified pipeline to a set of influenza virus samples from a cohort study provided a realistic picture of intrahost diversity and suggested the need for rigorous quality control in such studies.

**Briese, T. et al. 2015. Virome capture sequencing enables sensitive viral diagnosis and comprehensive virome analysis. *mBio*.**

The system uses ~2 million probes that cover the genomes of members of the 207 viral taxa known to infect vertebrates, including humans. VirCapSeq-VERT enables detection of viral sequences in complex sample backgrounds, including those found in clinical specimens, such as serum, blood, and tissue.

The highly multiplexed nature of the system allows both the simultaneous identification and the comprehensive genetic characterization of all known vertebrate viruses, their genetic variants, and novel viruses.

The operational simplicity and efficiency of the VirCapSeq-VERT platform may facilitate transition of high-throughput sequencing to clinical diagnostic as well as research applications.



## The identification of new viruses brings a serious challenge



- Are these viruses pathogens or could they have symbiotic relationships with their host organisms?
  - *Are they “good for you?”*

- Do they stimulate local and systemic immune responses that protect us from infection by more virulent microbes?

Dissecting these relationships is providing unanticipated insights about viruses and their hosts.

Progress requires careful epidemiological and clinical studies aided in part by more advances in technology.

## So much data, so much to understand

**Proof of causation of disease can no longer rely on the time honored Koch's postulates.**



- it may be difficult to propagate new viruses and find models to test their pathogenicity
- many diseases will involve the interaction of multiple microbial communities (viruses, bacteria, fungi) that will be difficult to reproduce in the laboratory
- “new” human infections are likely to be zoonotic and not just from wild animals!



**Two Important, paradigm changing realizations that came primarily from deep sequencing**

**Microbiome:** *all of the organisms that live in or on the host: virome, bacterial microbiome, archaeal microbiome, mycobyome, meiofauna, others?*

**Metagenome:** *The sum of ALL of the genes in or on the host: host genes plus genes in the Microbiome.*

# The complex interaction of microbes and their hosts

Two excellent reviews:

**Cadwell, K. 2015. The virome in host health and disease. *J. Immunity*.**

**Virgin HW. 2014. The virome in mammalian physiology and disease. *Cell***

## My pick for one critical paper from 2016 on the virome

**Handley, S. A. 2016. The virome: a missing component of biological interaction networks in health and disease. *Genome Medicine*.**

Host-associated viral populations, viromes, have been understudied relative to their contribution to human physiology.

Viruses interact with host gene networks, influencing both health and disease.

Analysis of host gene networks in the absence of virome analysis risks missing important network information.



## THE CRYSTAL BALL

What is next???

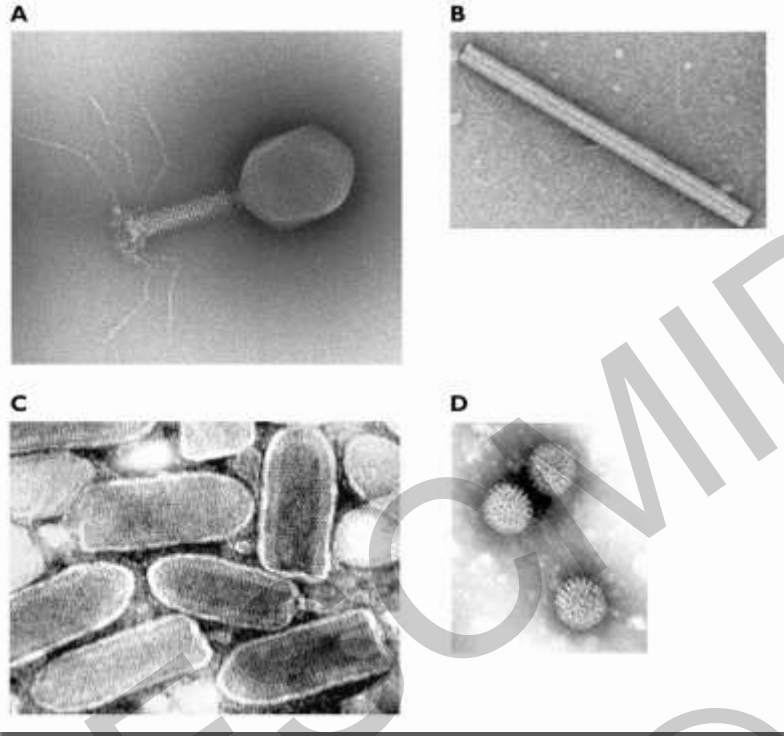
*These are exciting times for biology in general and for virology in particular*

The knowledge, techniques, new ideas, and urgency to learn more are stronger than ever.

The time from discovery to application is becoming shorter.

There are important forces at work that affect virology.

**We are at a seminal moment  
in the conduct of the life sciences,  
particularly virology**



**Some have concerns about  
biosafety and biosecurity of  
virology research**

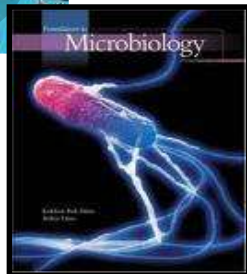
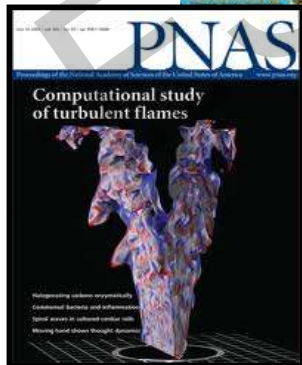
These concerns must be addressed

The public trust must be cultivated

**Fears, et al. 2016. European academies advise on  
gain of function studies in influenza virus research.  
*J. Virol.***

# The future of journals and traditional publications is not clear. *Scientific communication is changing*

Horton, R. 2016. Offline: the crisis in scientific publishing.  
*The Lancet*

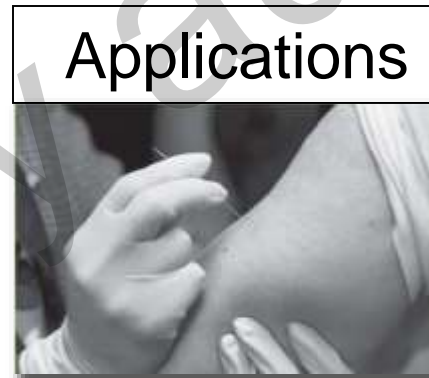


- No more print journals?
- Open access?
- Impact Factors: useful or useless?
- Peer review is outmoded?
- Blogs: Internet publications?
- Preprint servers – instant posting?



## The obvious drivers of virology research in the next decade:

- *Systems biology of virus-host interactions*
- *Viral ecology and the virosphere*
- *Evolution of viruses in the real world*
- *Efforts to improve vaccines and find new therapeutics*
- *Determining pathogenesis dynamics; zoonotic infections*
- *Population biology and public health*



**It is an exciting time to be a virologist!**

