



CANCER & EVOLUTION SYMPOSIUM

Boston, Massachusetts - October 14-16, 2020

Symposium website: www.cancerevolution.org

Symposium Purpose & Goals

October 14, 2020 – 8:30 am EDT

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Author, *Natural Evolution 4.0: Feedback-Driven and Actively Accelerated Biological Evolution*

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Let's start with a question: Would all the symposium speakers agree on these two basic statements?

- ❖ The insight that cancer is inherently a real-time evolutionary phenomenon has not yet entered mainstream oncology.
- ❖ There is no doubt anymore that cancers are *fundamentally* characterized by the parallel evolution of *heterogeneous, multiclonal cancer cell quasi-species*, interacting with the dynamic host tumor microenvironment and immune system.

Our overarching goal is to contribute to progress on sustainable, major improvements in outcomes for individual cancer patients, and to reduce and mitigate preventable cancer risks and incidence at a population health level.



CANCER & EVOLUTION SYMPOSIUM

Organization and Logistics

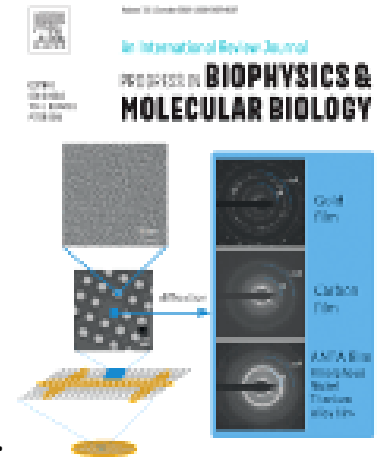
Introduction:

- ❖ Please adhere to the schedule and your speaking time slot precisely – this is essential for an on-line symposium.
- ❖ Questions submitted via Zoom ‘Chat’ will be addressed by the moderators and speakers, as time permits.
- ❖ This symposium will be recorded. All talks will be posted to a YouTube channel at the end of each day, where they can be accessed via www.cancerevolution.org. *If you do not want your talk to be posted, please let us know.*
- ❖ We are encouraging speakers and participants to be actively engaged for all three half days. The interactions during the talks and panel discussions will make this symposium more than the sum of all presentations.
- ❖ All participants will strive for constructive debate and consensus where possible, in order to gain new insights how to reprioritize cancer research, prevention, diagnostics and risk stratification, as well as crucial therapy improvements.
- ❖ In the two-week period after the symposium, selected speakers have scheduled voluntary Q&A sessions for interested participants, with times and login details available on the C&E Symposium website.

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Post-Symposium Outlook

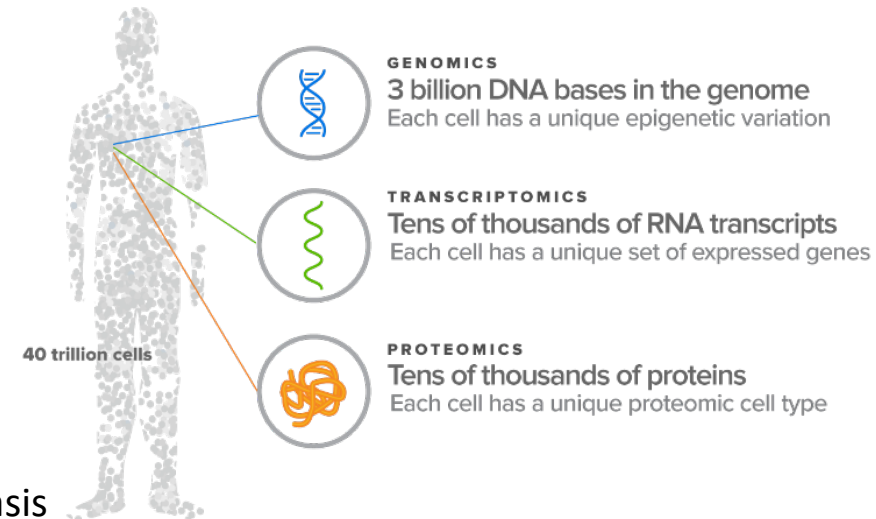
- ❖ We will publish graphical reviews of the symposium talks, panel discussions and recommendations in a Special Issue of *Progress in Biophysics and Molecular Biology* (Elsevier). Submission by Nov. 30, 2020.
 - *Graphical Reviews* are extended abstracts with explanatory figures from the presentation
 - Co-editor-in-chief Denis Noble has invited Paul Davies, Henry Henk, Ken Pienta and Jim Shapiro as *Guest Editors*.
- ❖ We plan to submit a scientific summary report as a ‘Scientific Perspective’ article, and a clinical impact report as a ‘Clinical Perspective’ article to a respected medical journal.
- ❖ We will issue a post-symposium scientific press release to interested science and medicine journalists and writers.
- ❖ This symposium could mark an inflection point with far-reaching ramifications for oncology and cancer patients.
- ❖ A monthly *Cancer & Evolution* lecture series and discussion forum may be established following this 2020 symposium.
- ❖ An in-person second symposium on *Cancer & Evolution* is anticipated for the fall of 2021.
- ❖ We may form a new *Cancer & Evolution Society*, or we may evolve into a *Cancer & Evolution* interest group with a satellite meeting at a larger cancer meeting or scientific conference.



Purpose and Goals of the Cancer & Evolution Symposium

Improved Understanding of Cancer Cell Evolution

- ❖ Bring together thought leaders, oncologists and out-of-the-box thinkers in cancer and organismal evolution, as well as in cancer research, epidemiology, diagnostics and therapy
- ❖ Review gradual and punctuated **cancer cell** evolution at the **genetic, epigenetic and DNA genome level**:
 - somatic mutations: founder, driver and passenger mutations in proto-oncogenes (Ras, EGFR, HER2) and tumor suppressors (p53)
 - DNA insertions and rewrites via reverse transcription, viral or exosome vectors for major alterations in genes and DNA regulation
 - ‘Heritable epigenetics’ of unicellular cancer quasi-species, analogous to tissue differentiation in development (e.g. methylation)
 - Genome destabilization (aka genome ‘chaos’) and large-scale genome reorganizations, e.g. via *kataegis* (localized hypermutation) or *chromothrypsis* (clustered chromosomal rearrangements)
 - Functional 3D genome changes
 - Karyotype changes, including aneuploidies, polyploidy and even multinucleated cells
- ❖ Explore evolution of cancer cell **gene expression and phenotype inheritance**:
 - Cancer cell transcriptomics, fusion RNA genes, the ‘living RNA genome’
 - Cancer cell proteomics and post-translational modifications (PTMs)
 - Cancer cell peptidomics and discovery of novel ‘heritable’ surface neoantigens
 - Cancer cell ‘heritable’ glycosylation decoration, and shield against immune system
 - Cancer cell extracellular vesicles (EVs) and exosome role in invasiveness and metastasis





Purpose and Goals of the Cancer & Evolution Symposium

Improved Understanding of Host Response, Opportunities for Early Detection

- ❖ Explore real-time evolution/development of **host response** and **cancer modulation/suppression of immune response**:
 - Explore role of host genetic risk, carcinogens and chronic inflammation in triggering cancer mutations
 - Host immune response and immune phenotype (immune cell DNA hypermutation, epigenetic markers)
 - Malignancy-enabling stroma and extracellular matrix (ECM) changes in proteins, glycosylation and protein-protein interaction (PPI) networks
 - Can we leverage proteomic, glycomic, PPI and metabolic host markers of disease for early detection with higher sensitivity?
 - Proteomic and metabolic biomarkers of MRD, progression, therapy response or evolving therapy resistance
 - Biomarkers of evolution of cancer cell invasiveness and metastasis, e.g. by cancer-mediated TME immune suppression
- ❖ Explore implications of cancer evolution in **cancer early detection and diagnostics**:
 - Prevention, early detection and early intervention are key to dramatic progress in the *war on cancer*, and for the reduction of patient suffering and mortality at a societal scale.
 - An evolutionary perspective on cancer can advance how we prevent or delay cancer in aging societies, how medical researchers and clinicians can detect earlier.
 - Early detection enables oncology to treat patients earlier for more meaningful progression-free survival times and better outcomes
 - Precancerous and early stage I and II cancer signatures unlikely to be the same as evolved late stage MRD or recurrence markers



Purpose and Goals of the Cancer & Evolution Symposium

Improved Understanding of Therapy Strategies against Evolving Cancers

- ❖ Explore implications of cancer evolution for **cancer therapy**:
 - Will *maximum tolerated dose monotherapies* of advanced cancers, despite potential initial benefits, do predictable long-term harm to patients, as therapy resistance almost inevitably evolves?
 - ➔ Explore various **adaptive therapy strategies**
 - The treatment paradigm of not following up with secondary or tertiary chemo-, targeted or immunotherapies until after tumors begin to regrow, i.e. until 'extinction pressures' on residual cancer subclones have eased and cancer cell populations have stabilized, requires urgent improvements (after all, we accept antiviral cocktails to fight HIV)
 - ➔ Explore novel combination **extinction therapy strategies** (already used in childhood leukemia)
 - The combination of chemotherapy with radiation therapy represents an 'extinction pressure' strategy

History of Science Background: Organismal Evolution is Evolving

Modern Synthesis Incomplete or Inaccurate, Needs Conceptual Extensions or Major Revision

❖ Evolution in upheaval, as Modern Synthesis (MS) Theory is ‘stretched beyond its limits’ or ‘falsified’:

- Insistence on variation *only* by random, infinitesimal mutations, contradicted by major genome changes and rearrangements
- Emphasis on gradualism *only* not supported by punctuated fossil record, nor by DNA record of evolution, both with major leaps
- Active NGE and other natural induction processes can breach Weismann barrier over time to rearrange and rewrite DNA with successive, long-term protected genome fixations. Genes are slow, high-fidelity ‘followers’ of fast, short-term ‘molecular phenome evolution’.
- MS ignores concepts like evolution of evolvability, phenotypic plasticity, developmental constraints/bias, or niche construction;
- Insistence on distinct species created by allopatric speciation, when sympatric speciation and hybrids are common (not only in plants)
- Neo-Darwinism insistence on natural selection of the fittest *individuals* as *only* adaptive force (along with genetic drift), rather than as the major ‘creative force’ of evolution, and with need for incorporating also *multilevel group selection* concepts
- EvoDevo concepts needed to explain *mechanistic causation of changes in* phenotypic innovation, beyond just population genetics
- Rejection of Neo-Lamarckian adaptation, now repeatedly observed in multigenerational inheritance of epigenetic markers
- Inability to explain much of bacterial, viral and plant evolution with mobile genetic elements (MGEs), frequent horizontal gene transfer (HGT), symbiogenesis and cell fusions leading to a reticulated ‘tree of life’, even in vertebrates; many also observed in cancer evolution;
- Along with misguided ‘Central Dogma’, MS has fostered an excessively gene-dominated view of biology, which culminated in now debunked, popularized ‘Selfish Gene’ concept. While evolution remains gene-centric, multi-causal systems emphasis is needed on:
 - Epigenetics, including multi-generational, short-term evolution of acquired traits
 - Gene networks, 3D genome and karyotype structures and function
 - Transcriptome with splice variants, post-transcriptional modifications, capability of reverse transcription, viral RNA-to-RNA replication
 - Proteome with dynamic and complex PTMs, protein-protein interactions, and protein complexes
 - Other information-carrying, short-term evolvable molecules, molecular complexes and molecular/cellular interactions in systems biology



Evolution is Evolving!

New Extended Evolutionary Frameworks Are Expanding or Replacing the *Modern Synthesis* in Unicellular and Multicellular Organismal Evolution

❖ Many names for the new framework, but there is substantial overlap and increasing agreement:

- 'Altenberg 16' meeting (2008)
- Massimo Pigliucci and Gerd B. Müller (editors): *'Evolution, the Extended Synthesis'* (2010)
- James Shapiro: *Natural Genetic Engineering (NGE)* in *'Evolution – A View from the 21st Century'* (2011)
- The Third Way of Evolution: <https://www.thethirdwayofevolution.com> (2014)
- Perry Marshall: *'Evolution 2.0: Breaking the Deadlock Between Darwin and Design'* (2015)
- Kevin Laland et al.: *'The extended evolutionary synthesis: its structure, assumptions and predictions'* (2015)
- Denis Noble: *Genome as an Organ of the Cell* in *'Dance to the Tune of Life. Biological Relativity'* (2016)
- Henry H. Heng: *'Genome Chaos: Rethinking Genetics, Evolution, and Molecular Medicine'* (2019)
- Frank H. Laukien: *Evolution of Evolutionary Processes and Evolvability beyond Genes & Genome* in manuscript *'Natural Evolution 4.0: Feedback-Driven and Actively Accelerated Biological Evolution'* (2020)
- *'Evolving Evolution'*, cover story in *New Scientist* (26 September 2020)



Agenda

Day One

Session
Chair
Frank
Laukien

Day One	Presentations	Speaker	Time
8:30 AM	Overview and Purpose of the Cancer & Evolution Symposium	Frank Laukien	15 min
8:45 AM	The Patient Perspective on Modern Cancer Therapy	Azra Raza	25+5 min
9:15 AM	What Can Evolutionary Biology Learn from Cancer Biology?	James Shapiro	25+5 min
9:45 AM	Break		15 min
10:00 AM	Accelerated evolution, proliferation & mammalian development/cancer	George Church	25+5 min
10:30 AM	Genome Chaos: creating new system information to drive macroevolution	Henry H. Heng	25+5 min
11:00 AM	A Systems-Approach to the Early Diagnosis and Prevention of Disease	Leroy Hood	25+5 min
11:30 AM	Break		15 min
11:45 AM	Single cell-based Analysis of cancer and host proteome interactions by Deep Visual Proteomics	Matthias Mann	25+5 min
12:15 PM	Harvard Origins of Life Initiative: Building Blocks, Protocells & UV-driven Evolution	Dimitar Sasselov	15 min
12:30 PM	Cancer evolution, immune evasion and metastasis	Charles Swanton	25+5 min
1:00 PM	Break		5 min
1:05 PM	Panel Discussion of Day 1: Insights and Controversies Panel members: Speakers of day 1	Co-Moderators: Frank Laukien Jeffrey Townsend	
1:45 PM	Day One Adjourn	Frank Laukien	



Agenda

Day Two

**Session Chair
James Shapiro**

Day Two	Presentations	Speaker	Time
8:30 AM	The Post-Modern Synthesis Movements in Organismal Evolution	James Shapiro Denis Noble	15 min
8:45 AM	The Next Challenge in Precision Cancer Medicine: Evolutionary Cancer Biomarkers	Anna Barker	15 min
9:00 AM	Cellular Darwinism: regulatory networks, stochasticity, and selection in cancer development	Denis Noble	25+5 min
9:30 AM	Can Adaptive Cancer Therapy Reduce Evolutionary Pressures?	Robert Gatenby	25+5 min
10:00 AM	Break		15 min
10:15 AM	Extracellular Vesicles in Metastasis, and Their Evolutionary Aspects	Scott Bonner	15 min
10:30 AM	The Somatic Molecular Evolution of Cancer: Mutation, Selection, and Epistasis	Jeffrey Townsend	25+5 min
11:00 AM	Reverting to single-cell biology in cancer	Paul Davies Kimberly Bussey	25+5 min
11:30 AM	Break		15 min
11:45 AM	Convergent Evolution and the Origins of Lethal Cancer	Kenneth Pienta	25+5 min
12:15 PM	Can the "Cancer Species" be driven to extinction?	William Audeh	15 min
12:30 PM	Cancer - Daring to Believe in a Cure and Why This Belief is Justified	Adelene Perkins	15 min
12:45 PM	The Evolution of Complex Traits in Diverse Populations	Michael Campbell	15 min
1:00 PM	The Evolution of Cancer Suppression Across Life	Carlo Maley	15 min
1:15 PM	Break		5 min
1:20 PM	Panel Discussion of Day 2: Insights and Controversies Panel members: Speakers of day 2	Co-Moderators: James Shapiro, Kenneth J. Pienta	
2:00 PM	Day Two Adjourn	James Shapiro Kenneth J. Pienta	



Agenda

Day Three

Session
Chair
Perry
Marshall

Day Three	Presentations	Speaker	Time
8:30 AM	Cellular Cognition and the Volitional Turing Machine	Perry Marshall	15 min
8:45 AM	Mechanisms of Malignant Progression of Carcinoma Cells	Robert Weinberg	25+5 min
9:15 AM	The Giant Cell Unifies Cancer Evolution, Development, and Human Life Cycle	Jinsong Liu	25+5 min
9:45 AM	Can Organismal Pattern Homeostasis Suppress Cancer?	Michael Levin	15 min
10:00 AM	Break		15 min
10:15 AM	Cancer Proteogenomics and Therapy Resistance	Michael Gillette	25+5 min
10:45 AM	Introducing Quantum Onco-Therapeutics: The Path to Memory T-cells	Patrick Soon-Shiong	25+5 min
11:15 AM	BoRs (Biomarkers of Response) To Optimize Metastatic Breast Cancer Treatment	Elizabeth O'Day	15 min
11:30 AM	RNA Whole-Transcriptome Sequencing in Cancer Diagnostics: Reducing Unnecessary Surgeries and Informing Treatment Decisions	Bonnie Anderson	15 min
11:45 AM	Break		15 min
12:00 PM	Cancer Cell Map Initiative: Interpreting cancer genomes with protein-protein interaction maps	Nevan Krogan	15 min
12:15 PM	The Evolution of Evolutionary Processes in Organismal and Cancer Evolution	Frank Laukien	15 min
12:30 PM	Mathematical Modeling of Cancer Evolution	Natalia Komarova	15 min
12:45 PM	The Role of 'Unnatural Evolution' in Cancer and Beyond	Steve Gullans	15 min
1:00 PM	Break		5 min
1:05 PM	Panel Discussion of Day 3: Insights and Controversies Panel members: Speakers of day 3	Co-Moderators: Perry Marshall Azra Raza	
1:45 PM	Next Steps and Recommendations <ul style="list-style-type: none"> - Publication of talks in Progress in Biophysics and Molecular Biology (Denis Noble) - Scientific Perspective article, e.g. for Science (Frank Laukien & Ann Barker) - Clinical Perspective article (Bill Audeh & Ken Pienta) - C&E Symposium 2021 or satellite meeting - C&E Society - stand-alone or within established society - Follow-on C&E Lecture Series & Discussion Group, C&E Website and Social Media Activities 	Organizing and Advisory Committees	30 min

