Adaptable, Flexible, or Novel: Regulatory Frameworks for Advanced Therapies

Case Study: Individualized Neoantigen-Specific Therapy (iNeST)

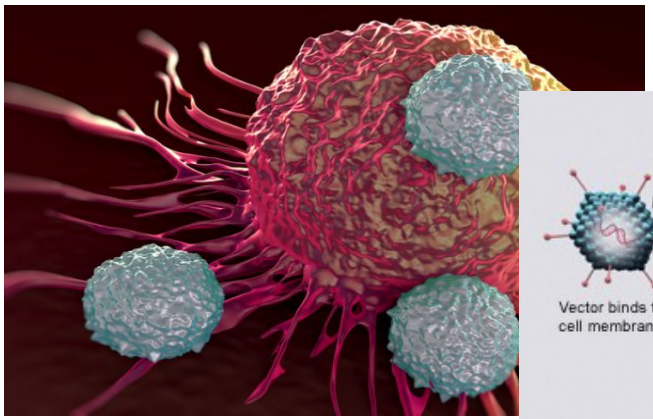
Kathleen Francissen, Ph.D.
Genentech, A Member of the Roche Group
28 January 2019
WCBP 2020 conference

Genentech
A Member of the Roche Group

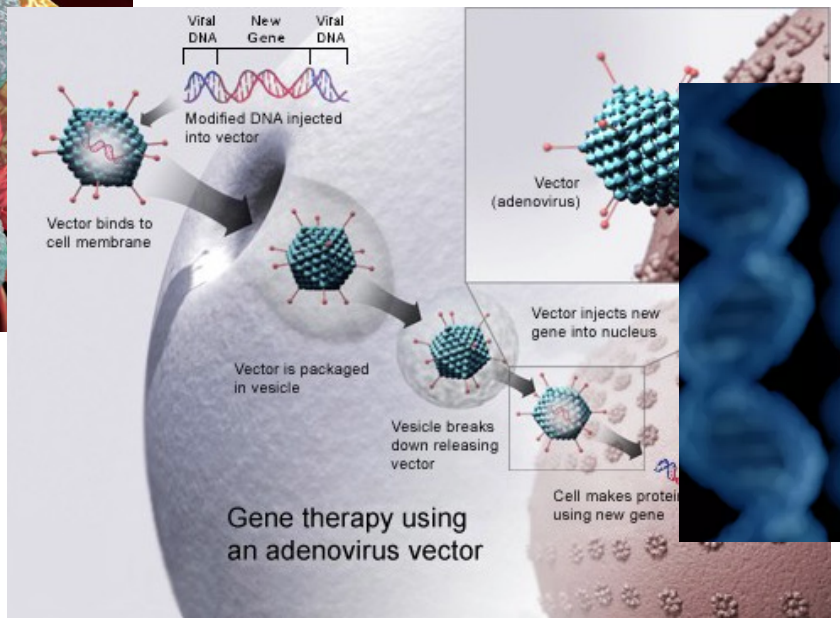
Cell and gene therapies include a wide variety of product platforms

Examples include…

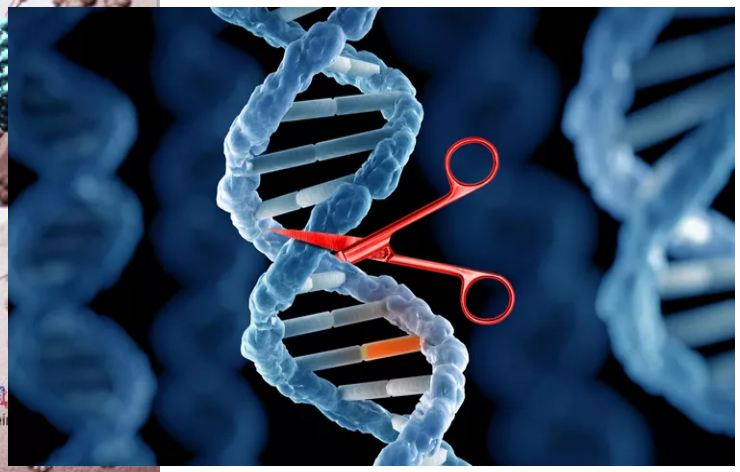
Cell-based Therapeutics



Gene Therapy Products



Gene Editing

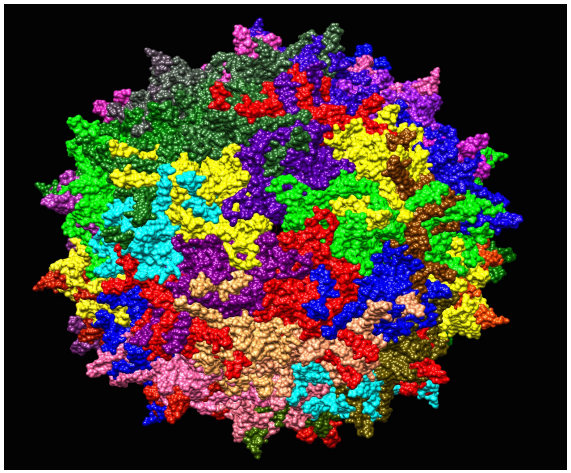


Gene therapies with viral vectors

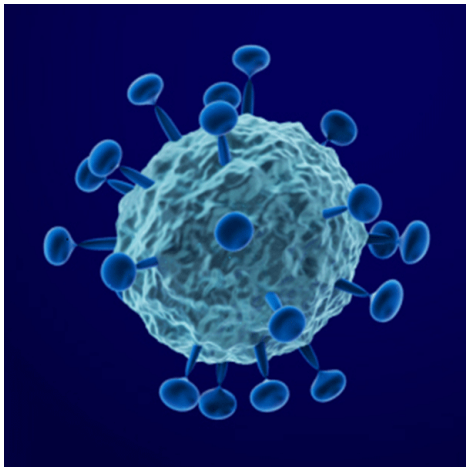
There are two main viral vectors used for gene therapies currently. They are:

AAV (adeno-associated virus): a small virus that infects humans but is not known to cause any disease. It is a small (20 nm), replication-defective, non-enveloped virus.

LV (lenti virus): a spherical enveloped retrovirus (80-100 nm). It can cause chronic and deadly diseases characterized by long incubation periods (most common HIV). It can integrate a large amount of cDNA into the host.



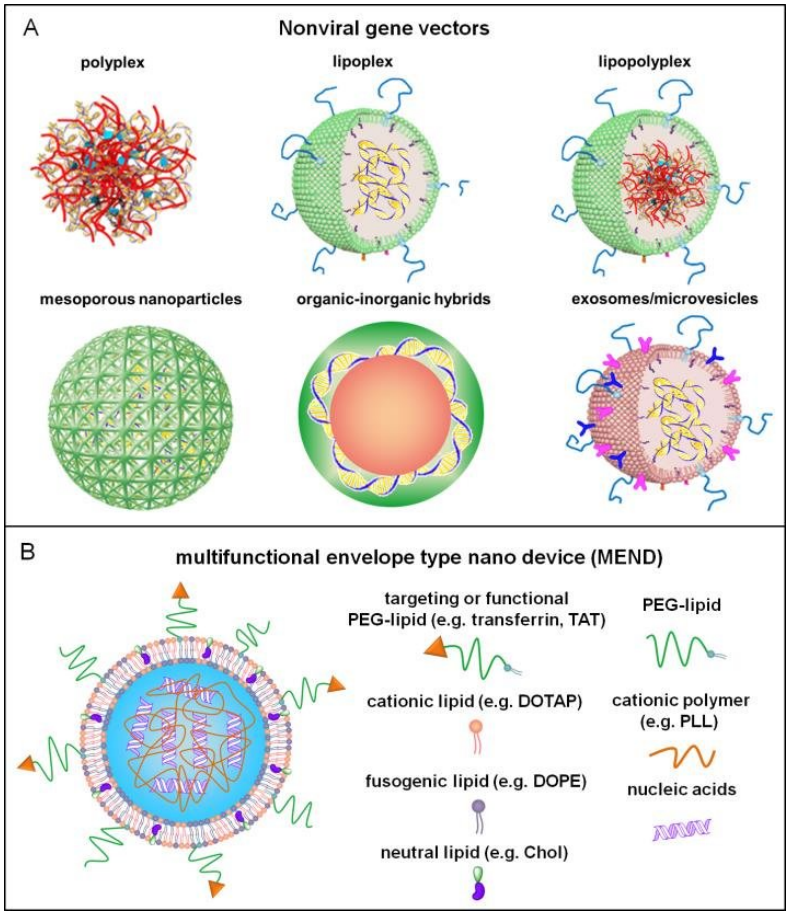
Adeno-associated Virus (AAV)



Lentivirus (LV)

iNeST

Gene therapies with non-viral vector systems



Nucleic acids: DNA and RNA

Liposomal formulations:
To protect the nucleic acid.
Can be made of lipids in an organized structure, like micelle or liposome

iNeST

Cell and gene therapies are fundamentally different than conventional medicinal products

- Some of them are individualized (made for a single patient) while others are produced for a group of patients
- Some require human tissue samples for their production, and others do not
- Some of them have unintended, but inherent variability while others have intended variability by design
- Different platforms of cell and gene therapy products have different challenges and requirements

Delivering cellular and gene therapies to patients: solutions for realizing the potential of the next generation of medicine, K. Elverium and Whitman, M. (April, 2019) Nature Reviews

iNeST

The rate of change is so fast that regulations struggle to keep up with technology

- “Without clear knowledge of the future potential or future unintended negative consequences of new technologies, it is nearly impossible to draft regulations that will promote important advances – while still protecting ourselves from every bad side effect.”
  - --Thomas Friedman (from “Thanks for Being Late”)

- The rapid pace of innovation and technological advances – requires rapid and focused development of solutions to move beyond old systems and ensure that appropriate patients can benefit from this new frontier of medicines…

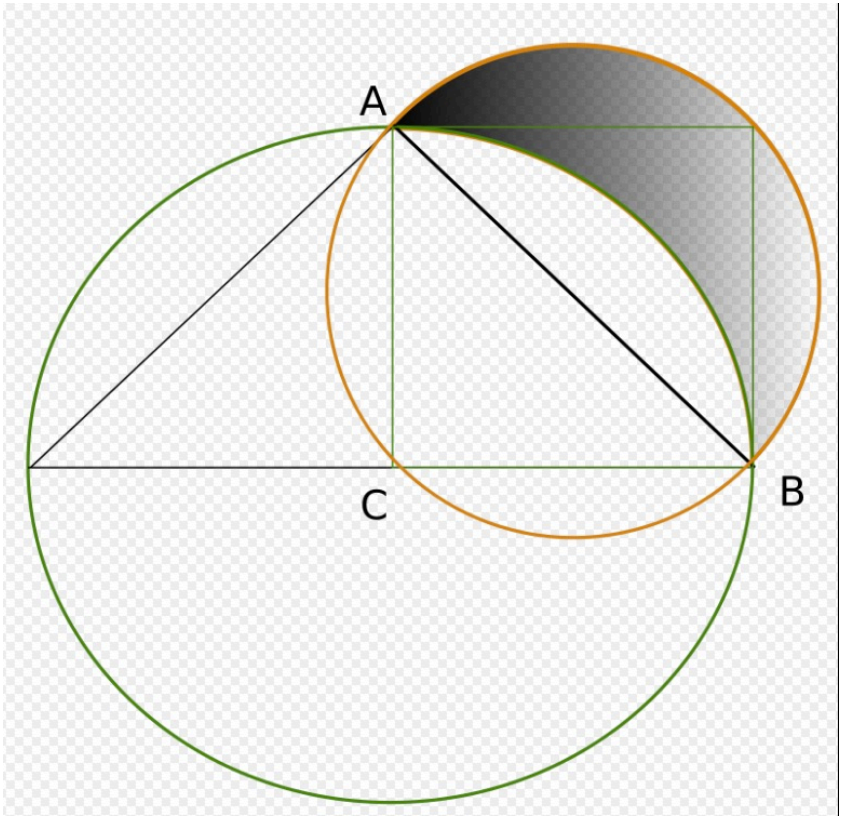
iNeST

Next generation medicines: Are we trying to fit square pegs into round holes?

Existing regulations were established for traditional medicinal products (small molecules and biologics)
-To apply them to new modalities, need **flexibility** (not leniency), so developers focus on *appropriate* controls

Some regulatory guidelines have served the biotech field well, and should be **adapted**

But in some cases, **novel** regulatory frameworks are needed.
-Manufacturers need a different mindset and need to work with regulators to re-write the rules



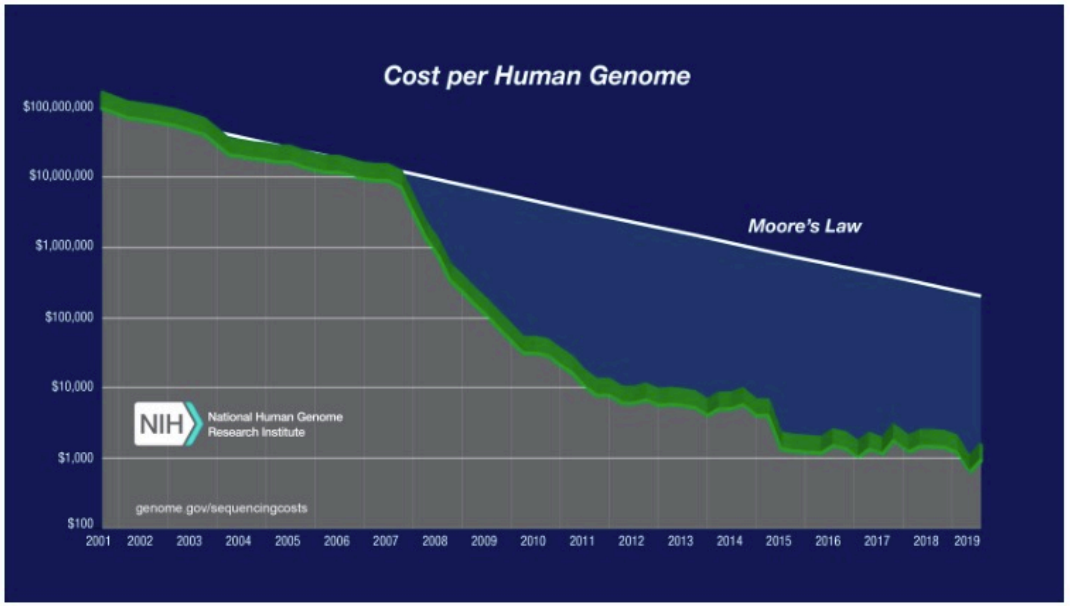
iNeST

Rapid and profound evolution in genome sequencing

The cost of sequencing the first whole human genome was about $2.7 billion in 2003 and took ~13 years to complete.

The cost decreased to about $1,000-3,000 in 2016 and takes one or two days.

* Many factors go into determining the cost of sequencing a genome.



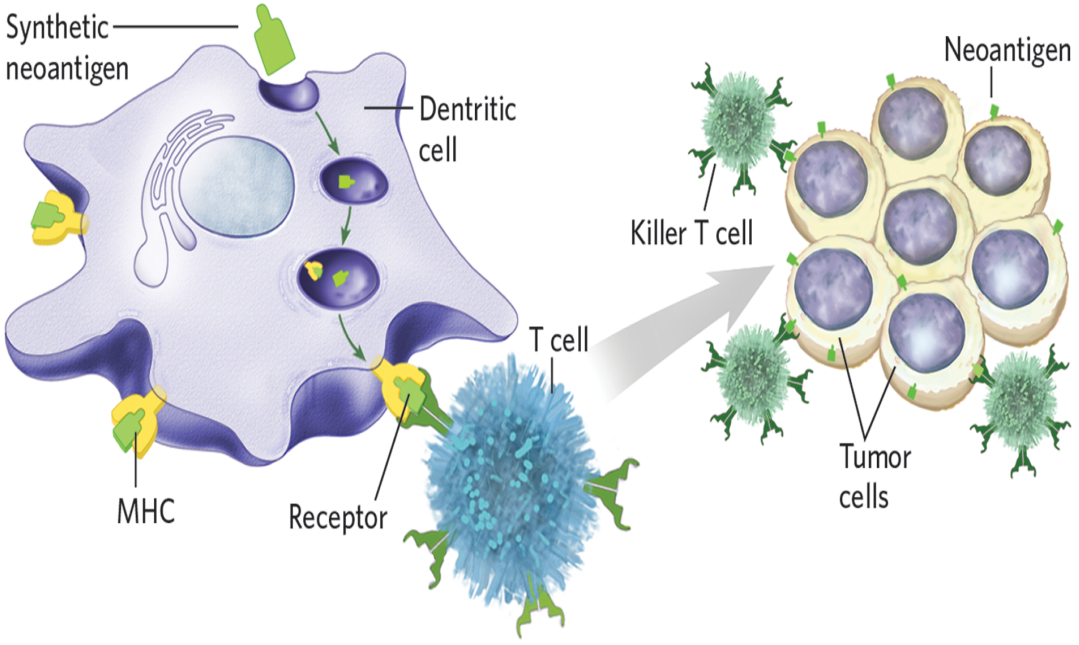
Cost per genome data

Advances in sequencing technology enabled neoantigen specific therapies

Neoantigen-specific immunotherapies (NeST) (also known as ‘cancer vaccines’) seek to mount a natural immune response to a cancer-specific (neo)antigen.

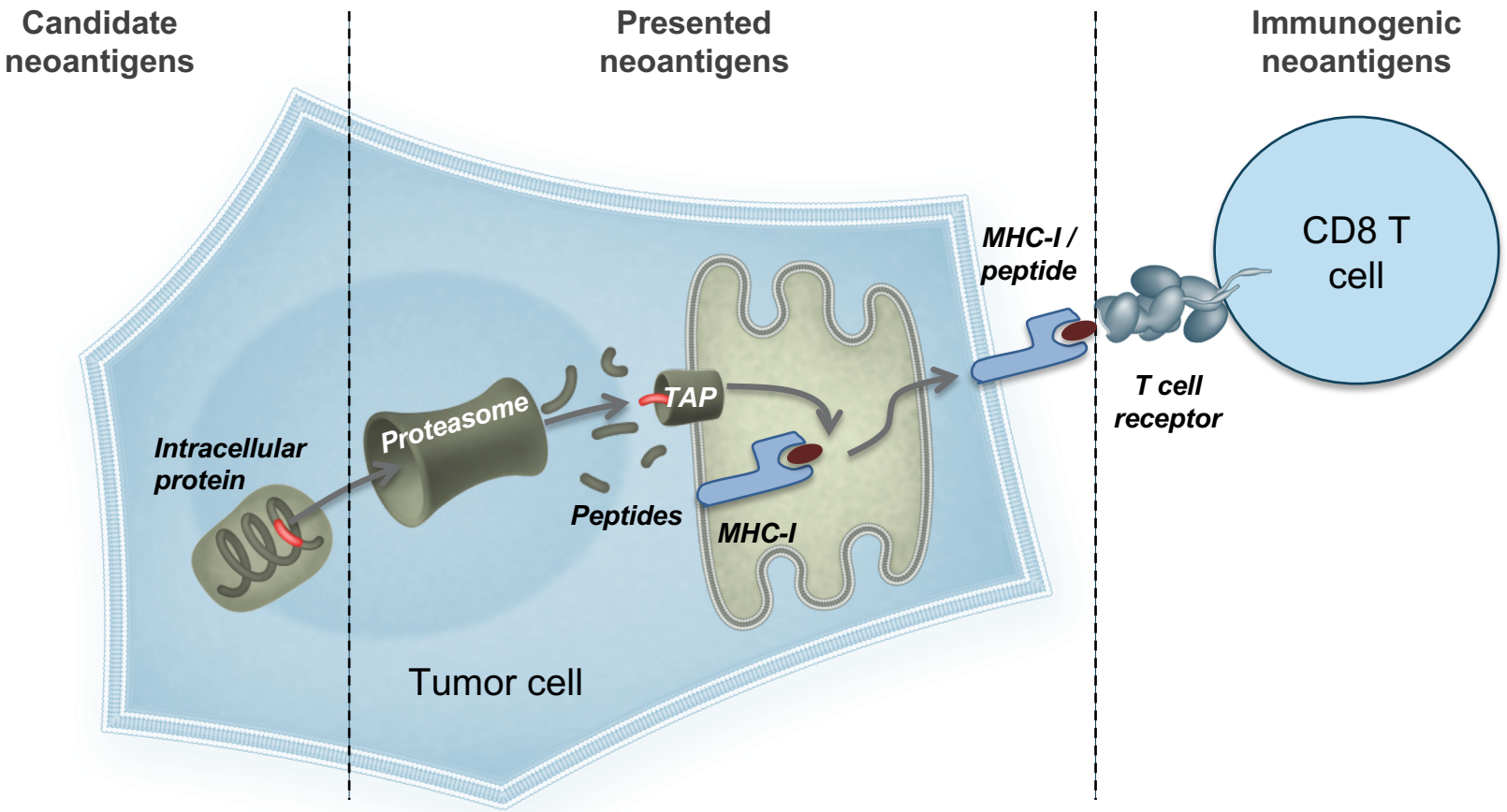
NeST can be cell-, protein-, or nucleic acid-based products

NeST ultimately deliver the neoantigen peptides that will activate a cell-mediated immune response.



iNeST

Immunogenic neoantigens result from processed and presented mutant peptide sequences recognized by T cell receptors



Class II presentation is also relevant; class II pathway not shown.

RNA and RNA-lipoplex manufacturing changes

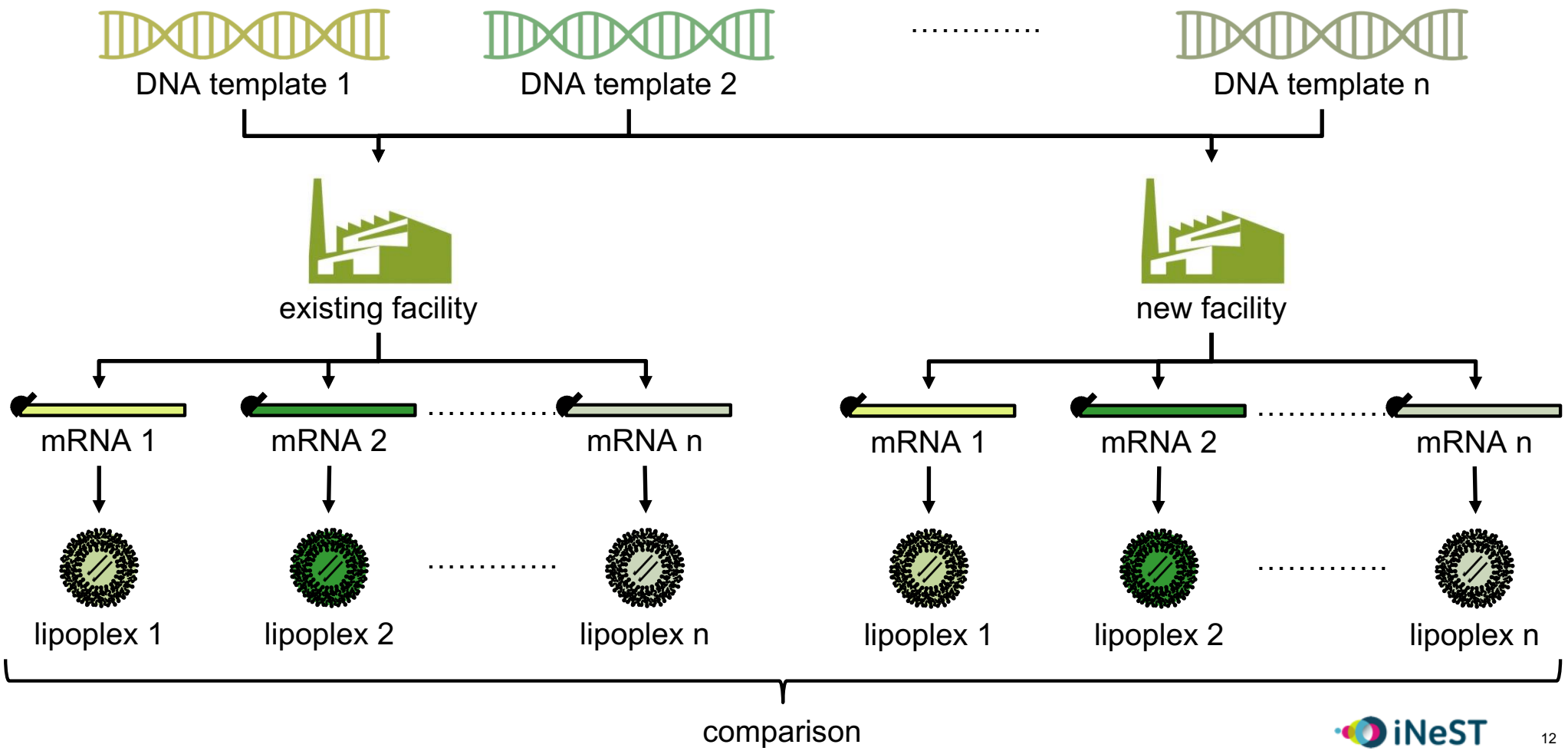
Comparability assessments as per ICH Q5E can be conducted, with some adaptation, to evaluate manufacturing process changes

- The RNA and RNA-lipoplex are relatively well characterized, which is a prerequisite for a meaningful analytical comparison of pre- and post-change product
- Since each patient's batch of mRNA has unique neoepitope sequences, need pairwise comparisons of batches.
  - Length and number of neoepitopes may also differ from batch to batch

- Addition of new GMP manufacturing facility: split the manufacturing stream from starting material (DNA template) to produce a pair of batches, which can be compared head-to-head

iNeST

Split-Stream Manufacturing: Pairwise Comparison of Batches



Considerations for point of splitting: DNA Templates

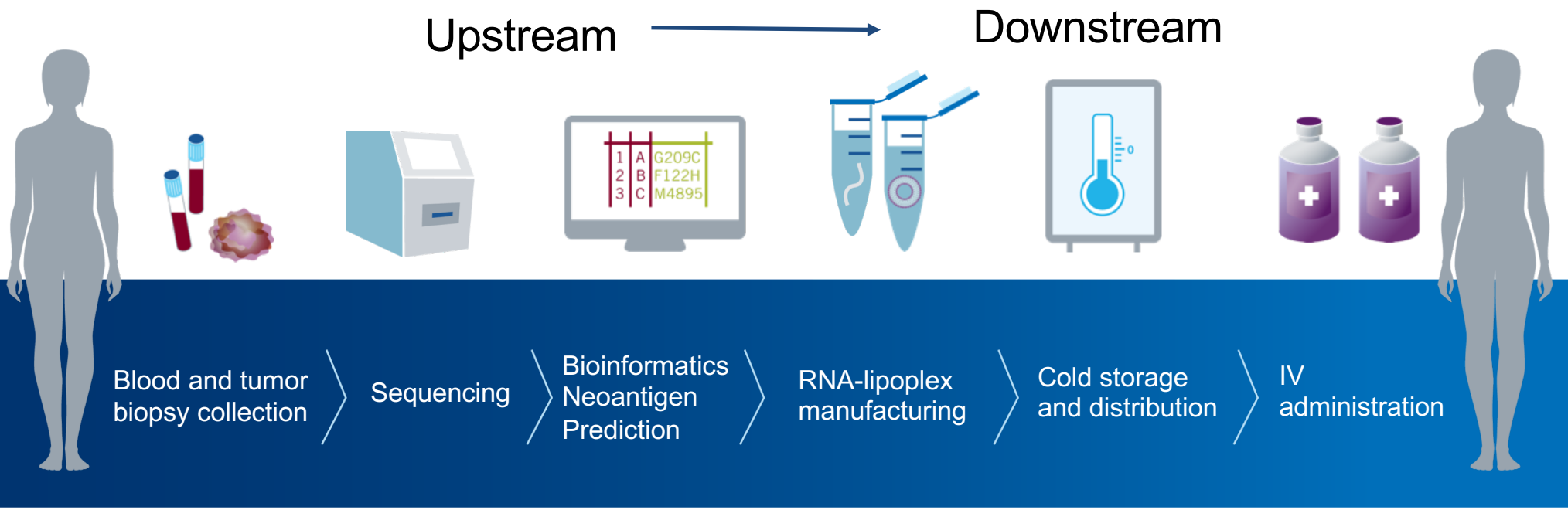
- Design of a set of sequences that bridge the sequence space of potential patient-specific sequences (including worst case and best case scenarios as well as typical sequences)
- Factors to take into considerations might include:
  - Sequence length (defined by number and length of individual neoepitopes)
  - GC-content (due to amino acid [and thus the corresponding codon triplet] distribution)

iNeST

Approach to assessing comparability: As per ICH Q5E

- Different levels, what to compare:
  - Drug substances (i.e. mRNAs) and drug products (i.e. lipoplexes)
  - Pair-wise comparison of mRNA and lipoplex batches from DNA templates 1, 2, …, and n
  - Comparison of pairs of mRNA and lipoplex batches from existing and new facility
- Parameters to compare:
  - Release testing of drug substance and drug product (e.g. RNA content, RNA integrity, particle size, potency) – within specifications and statistically determined ranges
  - Extended characterization (e.g. residuals not tested for every batch)
  - Stability (with initial read-out based on accelerated and stressed conditions)

iNeST: How to assess changes in upstream process



Close communication and coordination is required between manufacturing, clinical team and clinical sites

Evolution of Illumina sequencing-by-synthesis short read next-generation sequencing hardware

Genome Analyzer IIx
HiSeq 2000
HiSeq 2500
HiSeq X Series
HiSeq 3000/4000
NovaSeq Series

2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019

iNeST

Binding and presentation: evolution of Immune Epitope Database content and associated algorithms and software

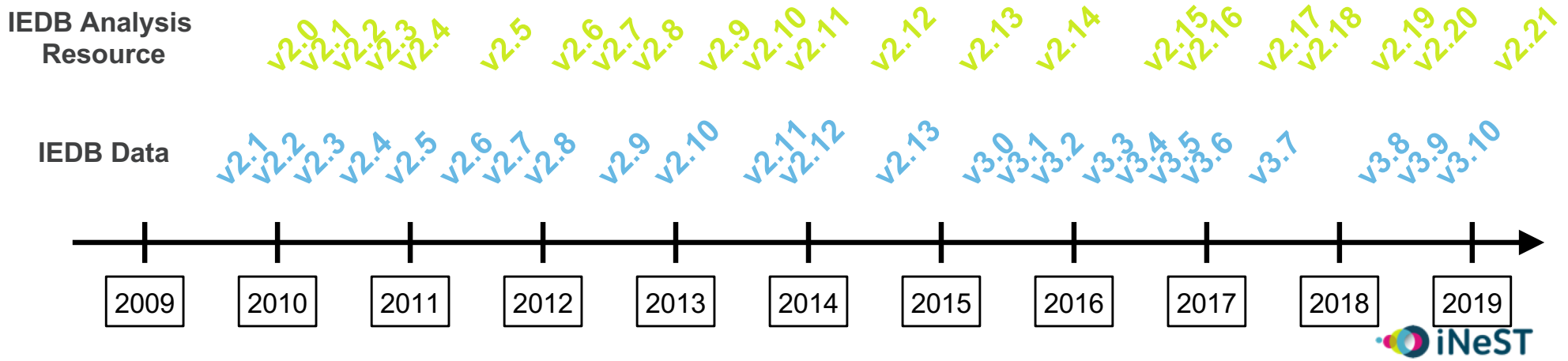
Published online 24 October 2018

Nucleic Acids Research, 2019, Vol. 47, Database issue ***D339–D343***
doi: 10.1093/nar/gky1006

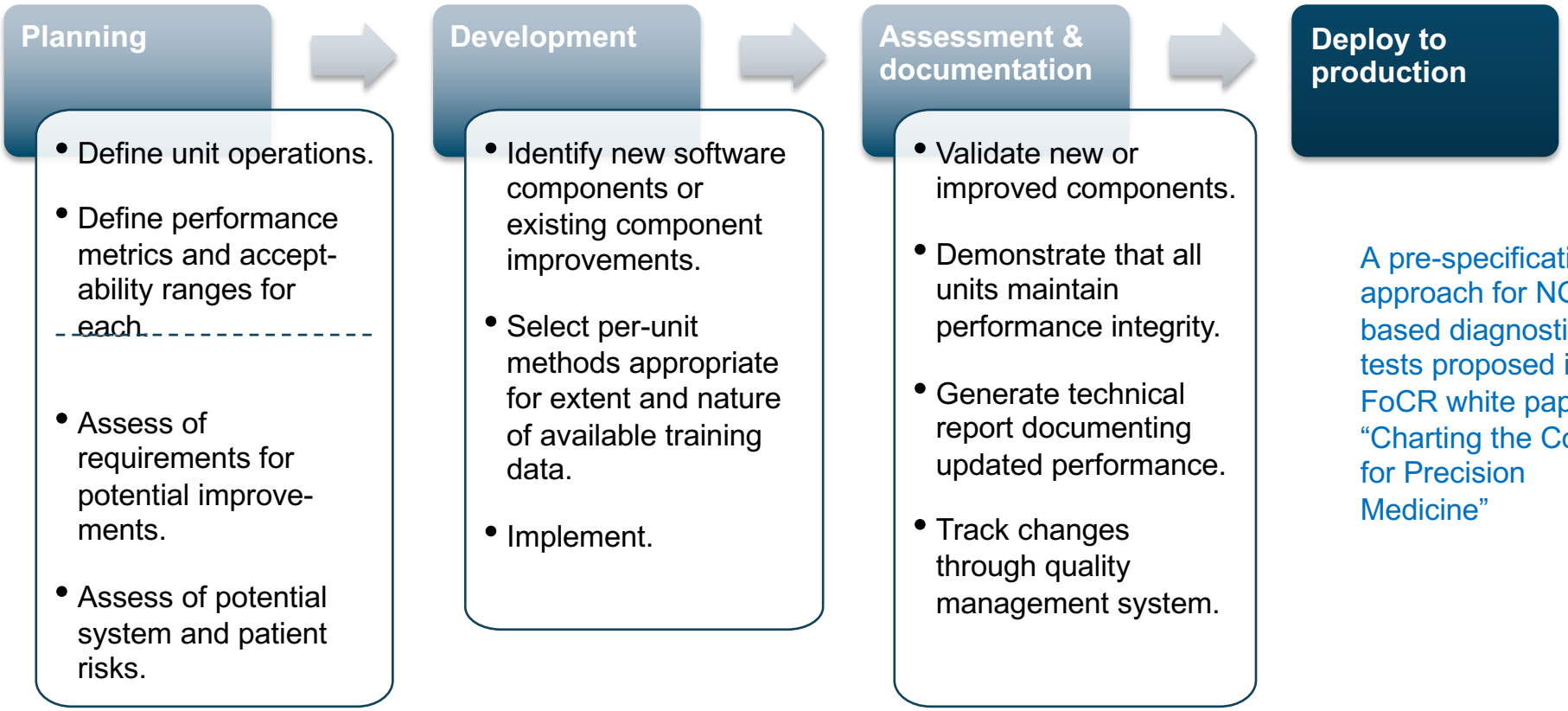
The Immune Epitope Database (IEDB): 2018 update

Randi Vita[1], Swapnil Mahajan[1], James A. Overton[2], Sandeep Kumar Dhanda[1], Sheridan Martini[1], Jason R. Cantrell[3], Daniel K. Wheeler[3], Alessandro Sette[1,4] and Bjoern Peters[1,4,*]

[1]La Jolla Institute for Allergy and Immunology, Division of Vaccine Discovery, La Jolla, CA 92037, USA, [2]Knocean Inc., Toronto, Ontario M2P 2T3, Canada, [3]Leidos Health, LLC, San Diego, CA 92121, USA and [4]University of California San Diego, Department of Medicine, La Jolla, CA 92093, USA



Pre-specified, unit-wise changes: a “do-and-tell” approach enabling timely improvements while providing transparency to regulators



A pre-specification approach for NGS-based diagnostic tests proposed in FoCR white paper “Charting the Course for Precision Medicine”

Updates in neoepitope selection steps (genome sequencing and bioinformatics) are fundamentally different than traditional process changes

-Analogous to analytical methods

-Based on *performance metrics*, rather than product comparability

iNeST

Novel regulatory framework for iNeST platform

Neoepitope selection process is considered part of production (and not a diagnostic)

- As agreed with US FDA and EMA and Health Canada
- Neoepitope selection process is initiated *after* a treatment decision has been made – required for design of each product batch
- Novel regulatory framework provides end-to-end visibility to regulators responsible for evaluating the safety and efficacy of final product

- Updates in genome sequencing and bioinformatics are fundamentally different than traditional process changes
  - Analogous to analytical methods
  - Based on *performance metrics*, rather than product comparability

iNeST

BIONTECH

Genentech
A Member of the Roche Group

Doing now what patients need next

iNeST