Moonshot International Symposium
Working Group 2

December 18th, 2019
Bellesalle Tokyo Nihonbashi

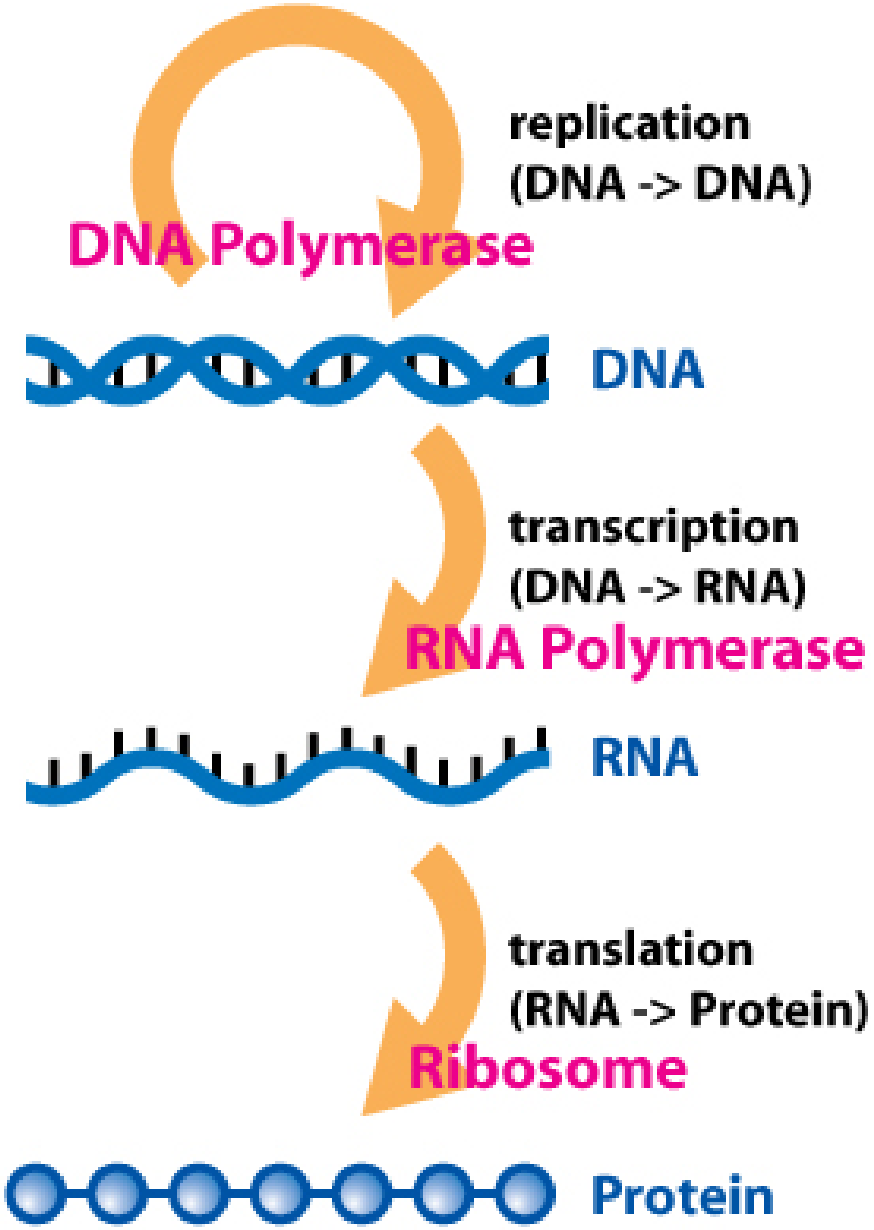
Recent Advances in Life Science towards a comprehensive understanding of organ networks

National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN)

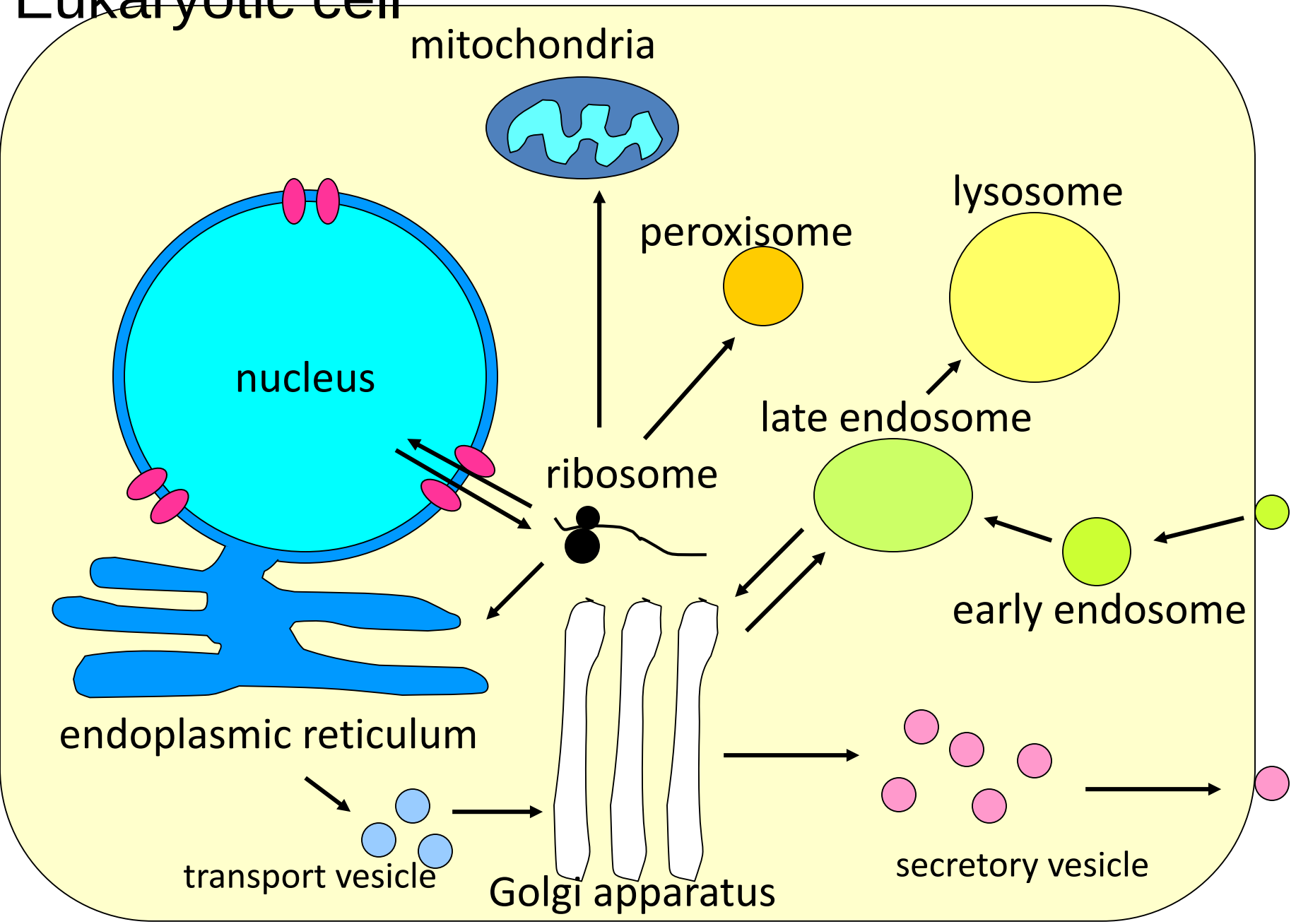
Yoshihiro Yoneda

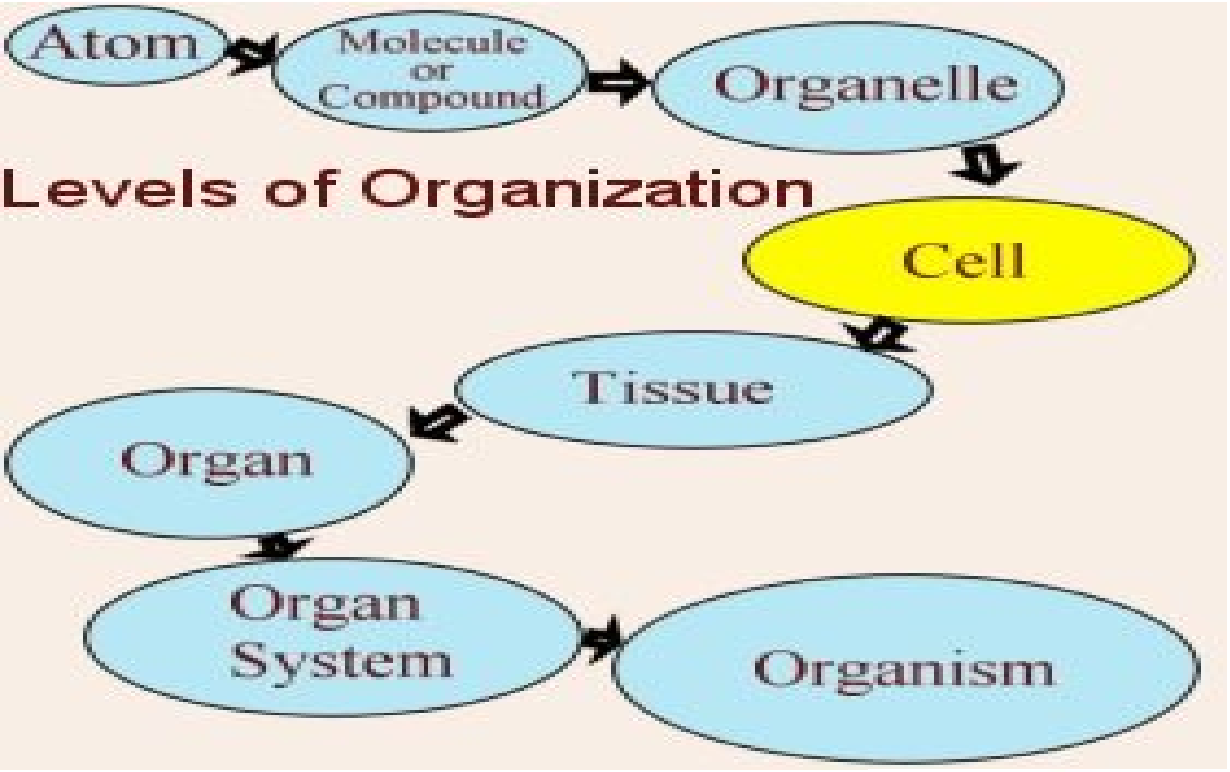
Towards a comprehensive understanding of organ networks

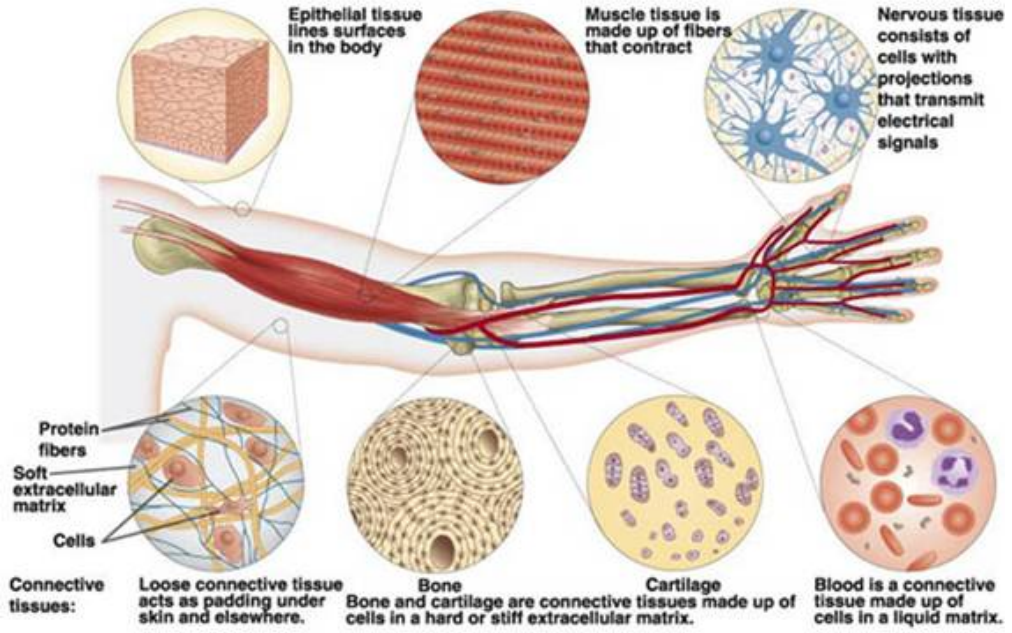
From basic principles of the biological system, and current progress and future prospects

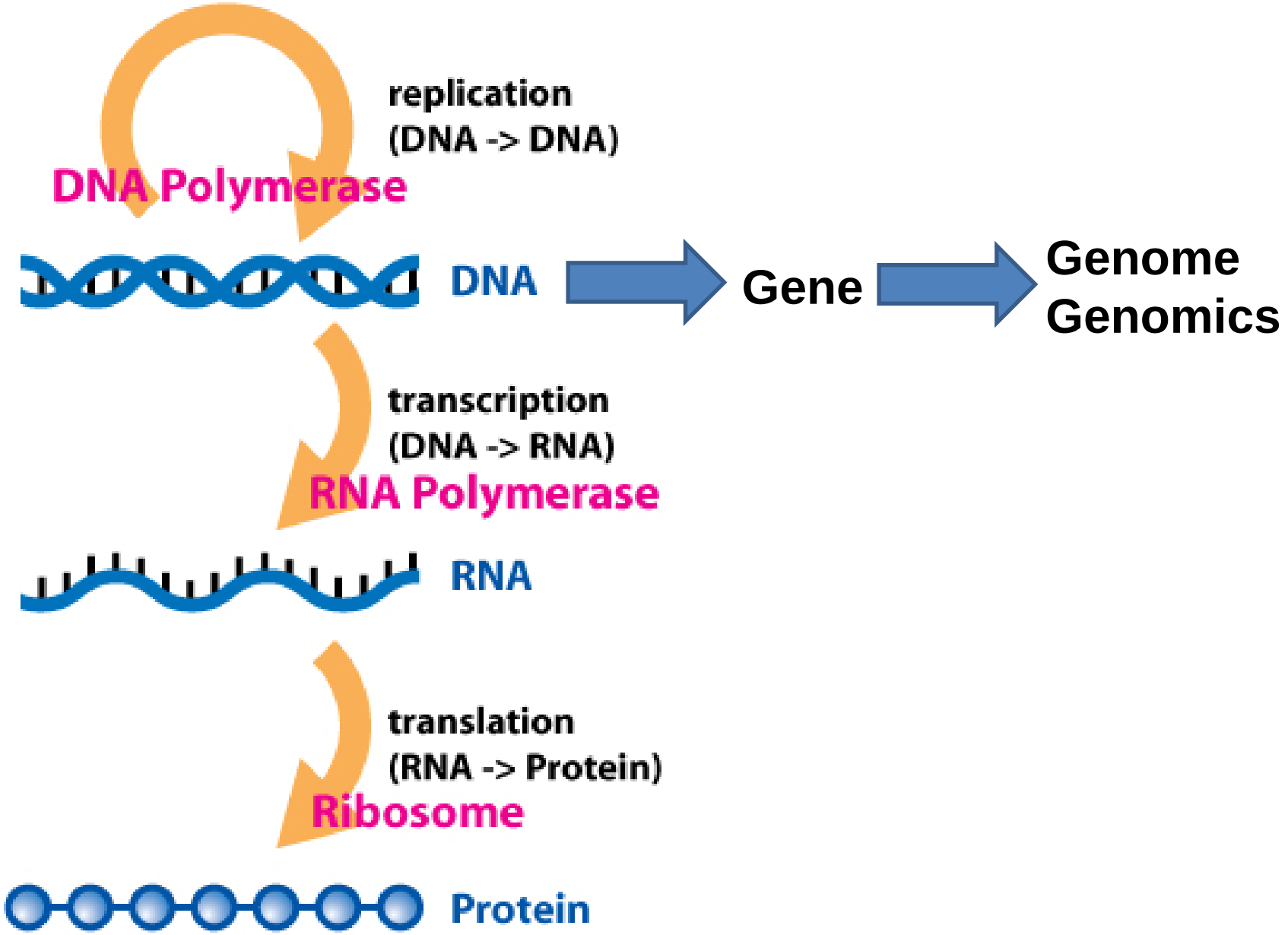

replication
(DNA -> DNA)
DNA Polymerase
DNA
transcription
(DNA -> RNA)
RNA Polymerase
RNA
translation
(RNA -> Protein)
Ribosome
Protein

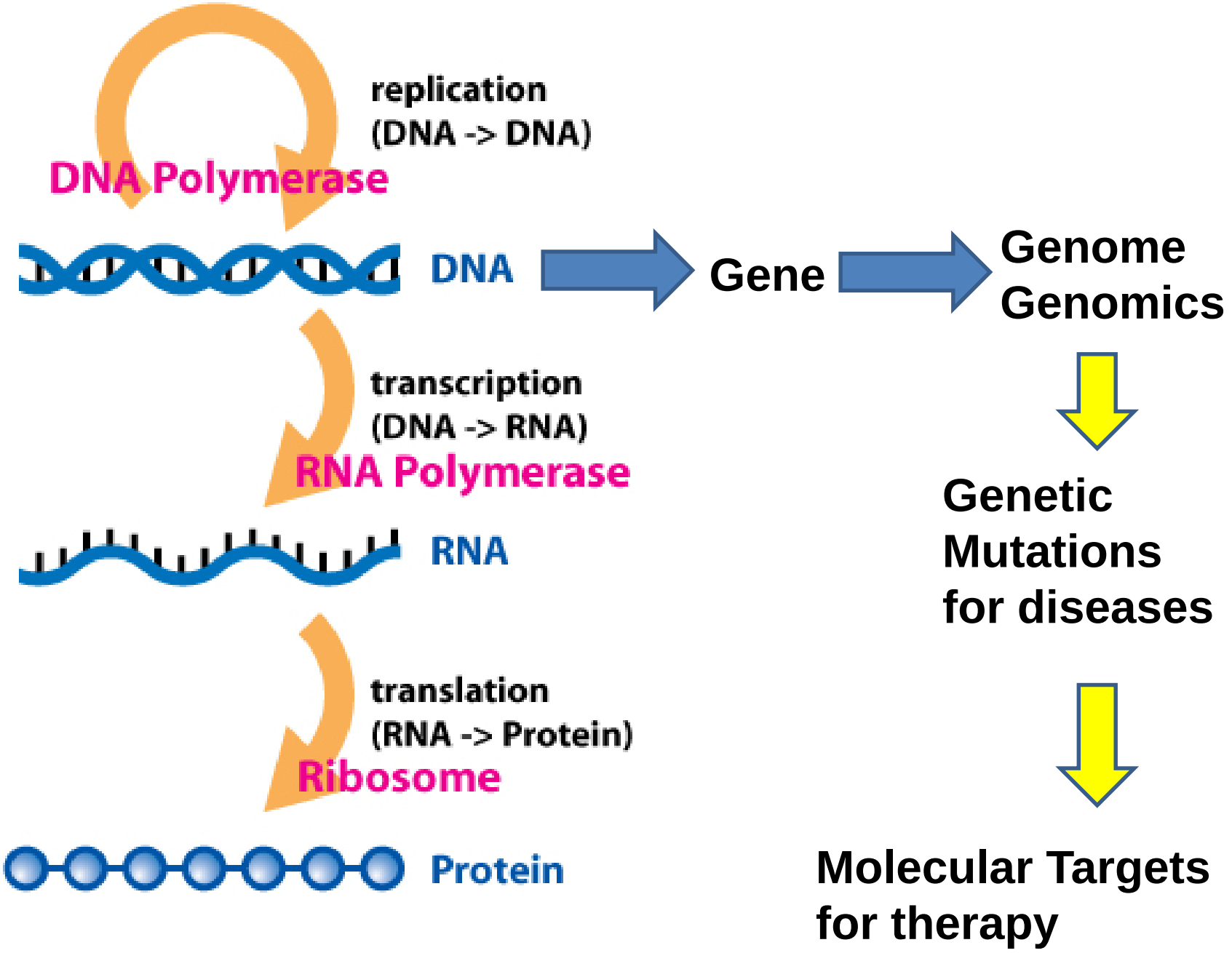
Eukaryotic cell

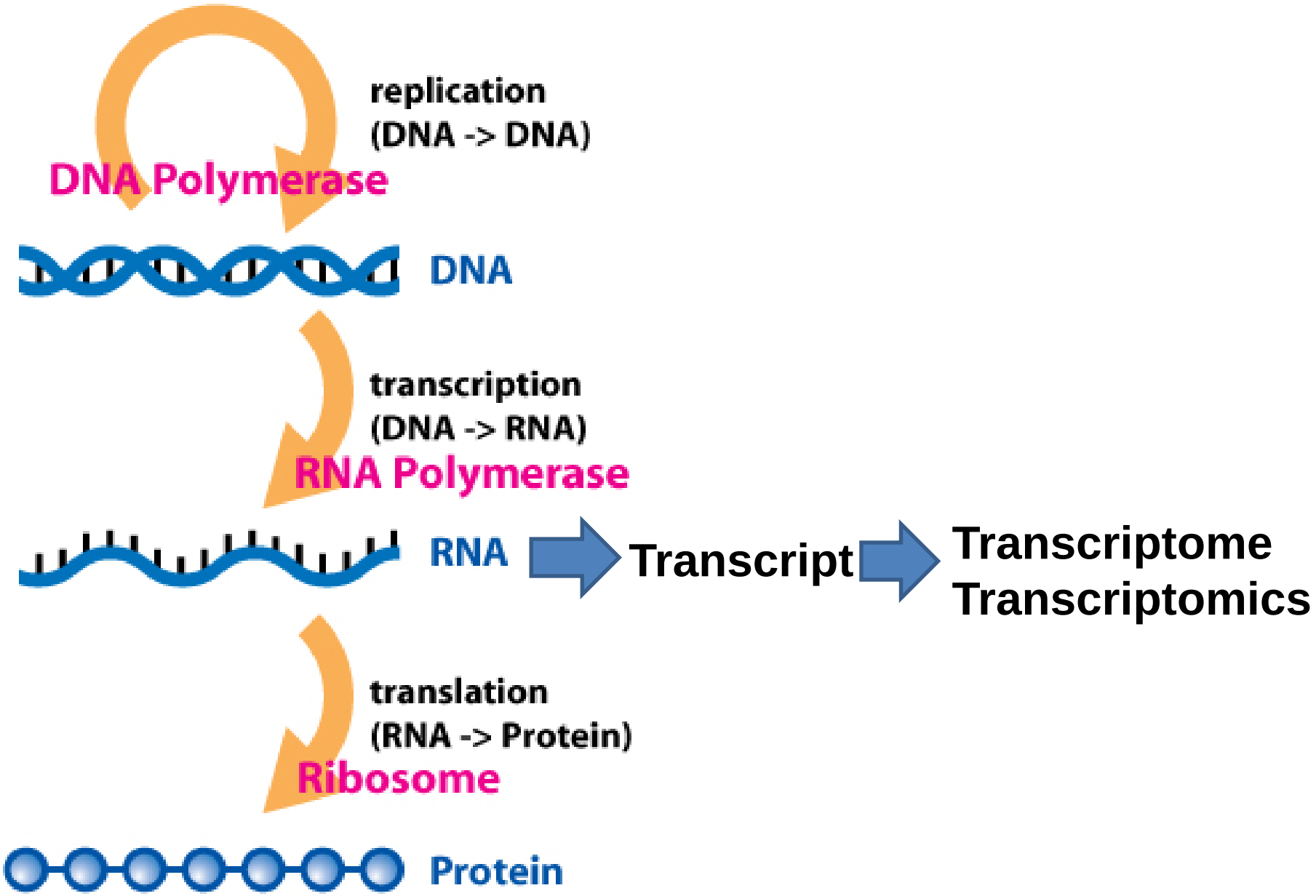



Atom
Molecule or Compound
Organelle
Levels of Organization
Cell
Tissue
Organ
Organ System
Organism


Epithelial tissue lines surfaces in the body
Muscle tissue is made up of fibers that contract
Nervous tissue consists of cells with projections that transmit electrical signals
Protein fibers
Soft extracellular matrix
Cells
Connective tissues:
Loose connective tissue acts as padding under skin and elsewhere.
Bone
Cartilage
Bone and cartilage are connective tissues made up of cells in a hard or stiff extracellular matrix.
Blood is a connective tissue made up of cells in a liquid matrix.


replication
(DNA -> DNA)
DNA Polymerase
DNA
Gene
Genome
Genomics
transcription
(DNA -> RNA)
RNA Polymerase
RNA
translation
(RNA -> Protein)
Ribosome
Protein


replication
(DNA -> DNA)
DNA Polymerase
DNA
Gene
Genome
Genomics
transcription
(DNA -> RNA)
RNA Polymerase
RNA
Genetic
Mutations
for diseases
translation
(RNA -> Protein)
Ribosome
Protein
Molecular Targets
for therapy


replication
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DNA Polymerase
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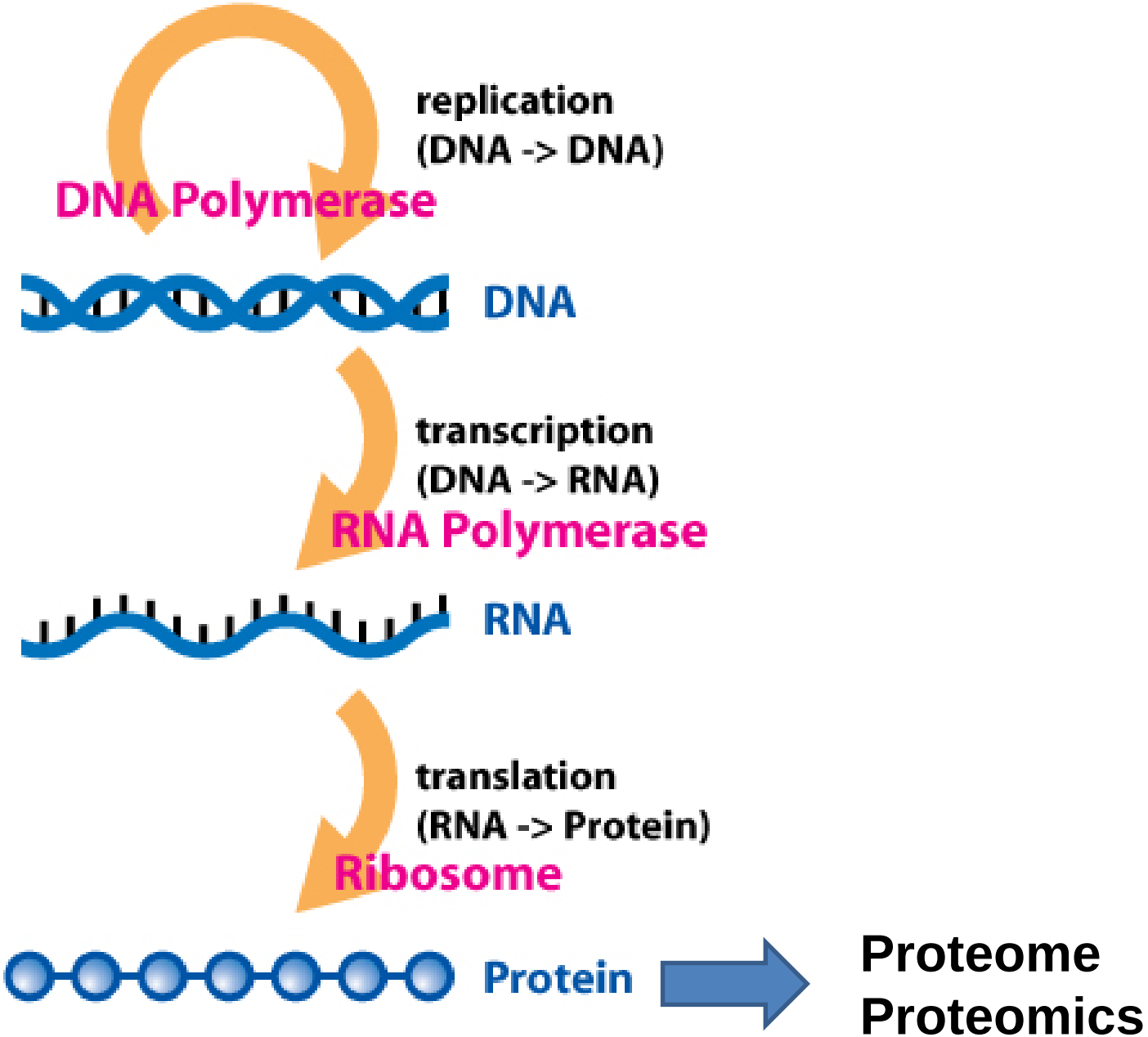
RNA Polymerase
RNA
Transcript
Transcriptome
Transcriptomics
translation
(RNA -> Protein)
Ribosome
Protein

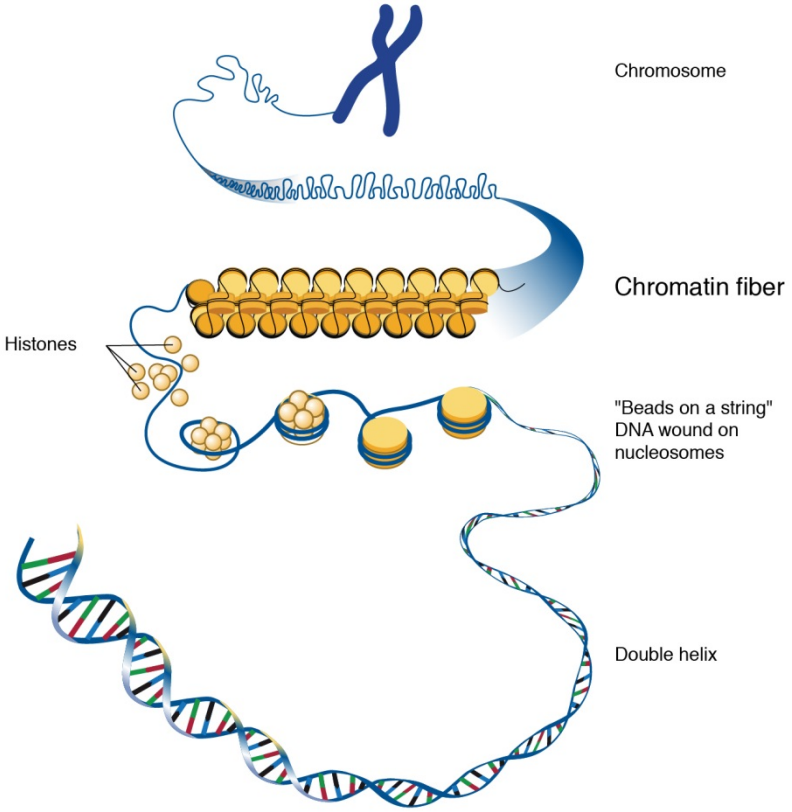


Proteome
Proteomics

Proteomics in conjunction with transcriptomics is used to investigate when and where proteins are expressed; rates of protein production, degradation, and steady-state abundance;
how proteins are modified (for example, post-translational modifications such as phosphorylation);
the movement of proteins between subcellular compartments;
the involvement of proteins in metabolic pathways;
how proteins interact with one another.
Proteomics can provide significant biological information for many biological problems, such as:
Which proteins interact with a particular protein of interest (for example, the tumour suppressor protein p53)?
Which proteins are localized to a subcellular compartment (for example, the mitochondrion)?
Which proteins are involved in a biological process (for example, circadian rhythm)?

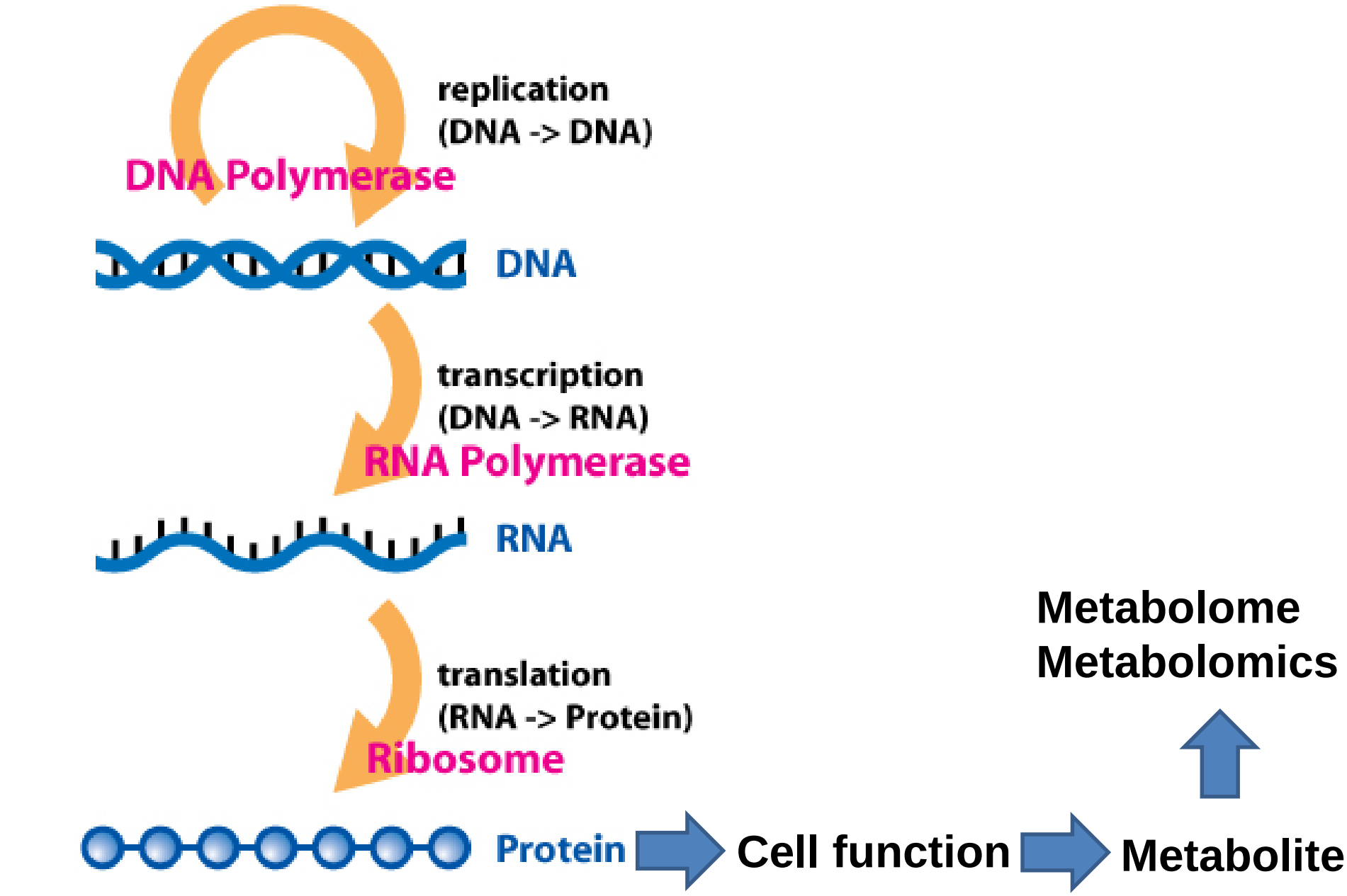
Proteomic technologies have advanced various areas of drug discovery and development such as the identification of biomarkers and molecular targets for therapy through the comparative assessment of normal and diseased-state tissues.

Epigenetics



Chromatin is a complex of DNA wrapped around histone proteins. Histones can be modified at their N-terminal tails by methylation, phosphorylation, acetylation, and ubiquitination as part of a histone signature serving to define accessibility to the DNA, that is, densely packaged “closed” chromatin (heterochromatin) in contrast to accessible “open” chromatin (euchromatin). Histone acetylation is known to be a predominant signal for active chromatin configurations while some specific histone methylation reactions are associated with either gene silencing or activation. These are regulated by histone modifying enzymes that catalyze the addition or removal of covalent modifications. This “histone code” can be “read” by specific proteins, which recognize certain histone modifications. Chromatin remodeling plays a central role in gene regulation by providing the transcription machinery with dynamic access to an otherwise tightly packaged genome.

Chromatin remodeling factors can be molecular targets for therapy.


replication
(DNA -> DNA)
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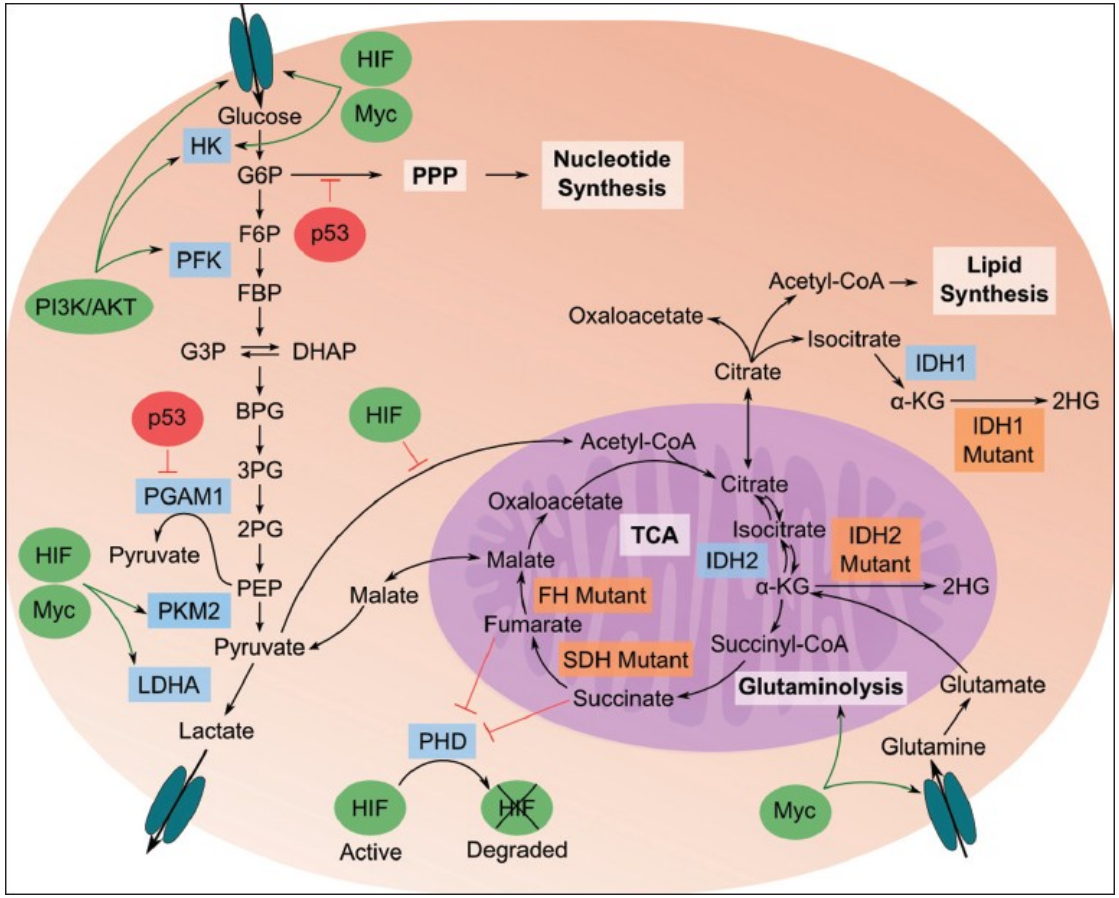
RNA
translation
(RNA -> Protein)
Ribosome
Protein
Cell function
Metabolite
Metabolome
Metabolomics

Tumor metabolome:

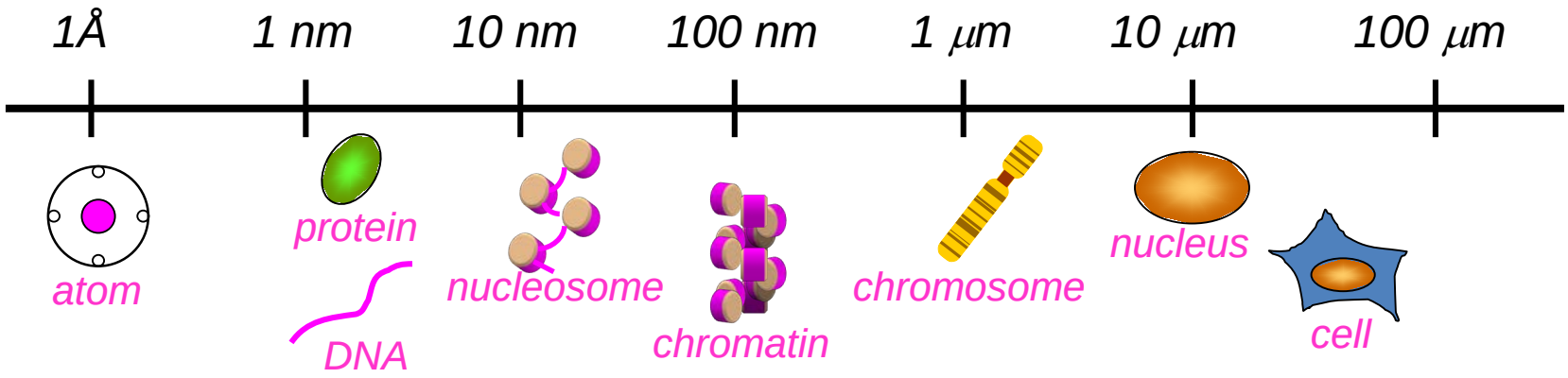


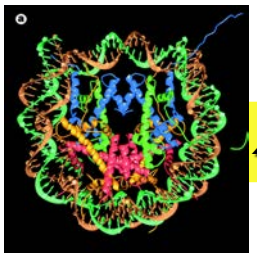
Blue boxes are enzymes important in transitioning to a cancer metabolic phenotype; orange boxes are enzymes that are mutated in cancer cells. Green ovals are oncogenes that are up-regulated in cancer; red ovals are tumor suppressors that are down-regulated in cancer.

Glycolysis breaks down glucose into pyruvate, which is then fermented to lactate; pyruvate flux through TCA cycle is down-regulated in cancer cells. Pathways branching off of glycolysis, such as the pentose phosphate pathway, generate biochemical building blocks to sustain the high proliferative rate of cancer cells.

Molecular Targets for therapy

From Nano to Micro

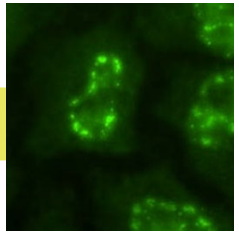




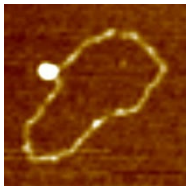
X-ray crystallography

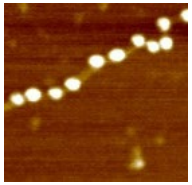
Cryo-electron microscopy

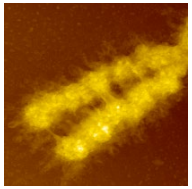
light microscopy

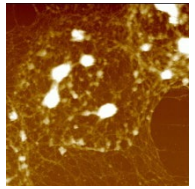


Electron Microscopy, Atomic Force Microscopy

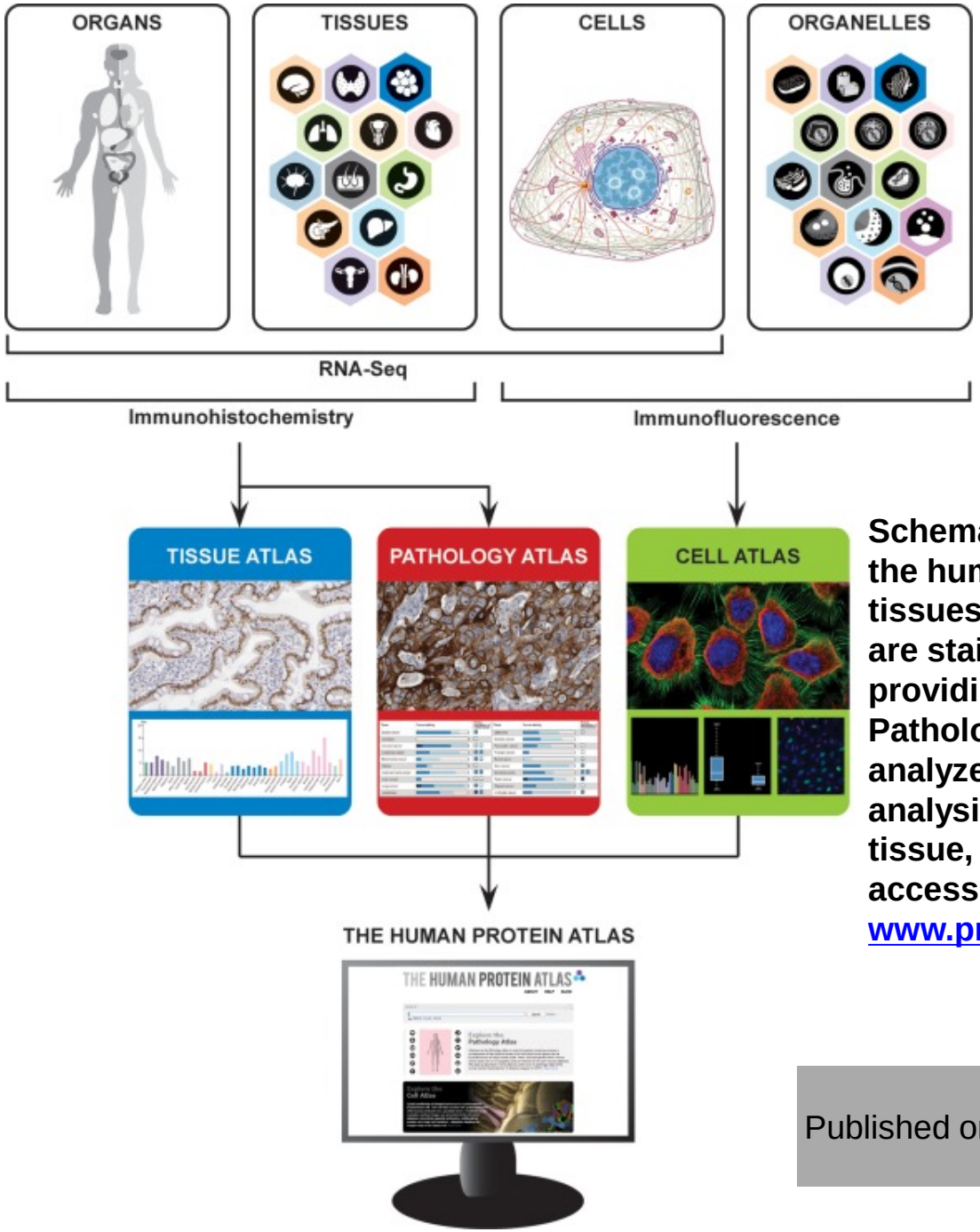






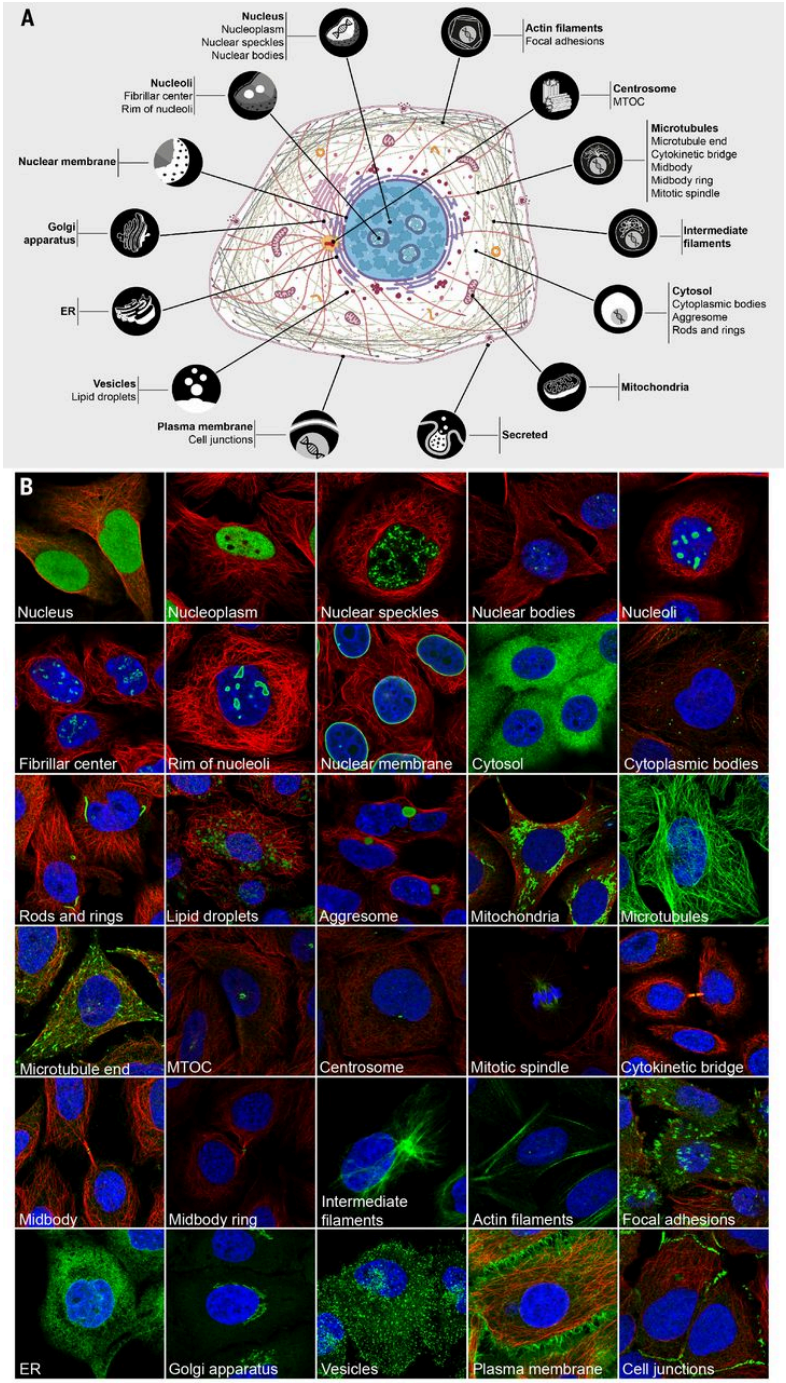


The human protein atlas: A spatial map of the human proteome



Schematic overview of the HPA. The HPA analyzes the human genome on different levels: in organs, tissues, cells, and organelles. Organs and tissues are stained using IHC (immunohistochemistry), providing the basis for the Tissue Atlas and Pathology Atlas, while cells and organelles are analyzed with IF in the Cell Atlas. The proteomic analysis is combined with RNA - Seq on the organ, tissue, and cellular level, and all data is freely accessible on the HPA web portal, www.proteinatlas.org.

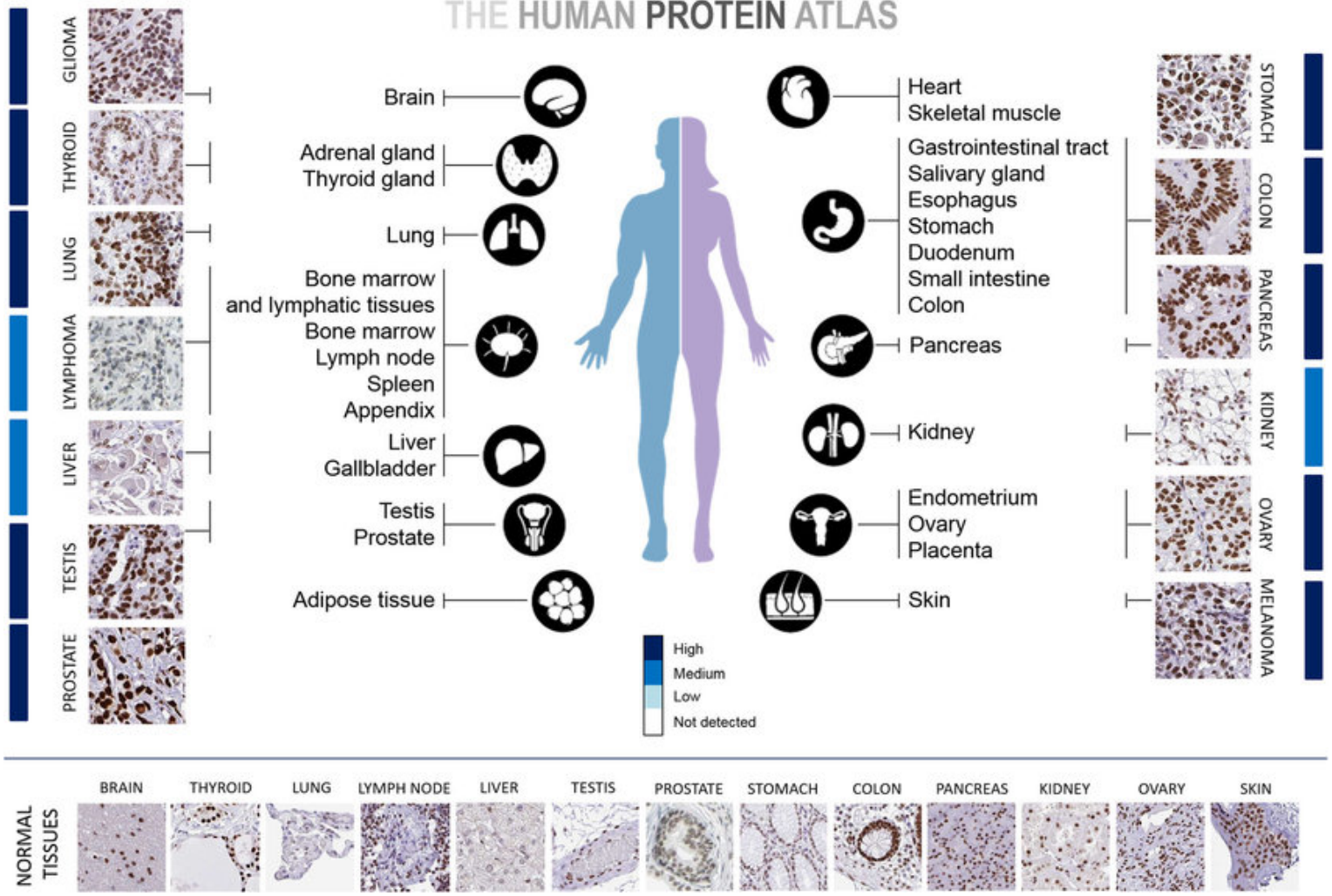
Protein Sci. 2018 Jan; 27(1): 233–244.
Published online 2017 Oct 10. doi: 10.1002/pro.3307
Peter J. Thul and Cecilia Lindskog



A subcellular map of the human proteome

Subcellular locations in the Cell Atlas.(**A**) Schematic overview of the cell. Thirteen subcellular proteomes, as well as a proteome of secreted proteins, were defined in the Cell Atlas by determining the localization of proteins to 30 subcellular structures. (**B**) Subcellular structures annotated in the Cell Atlas by immunofluorescence (IF) microscopy. Examples of proteins (green) localizing to each annotated structure in the representative set of human cell lines used in the Cell Atlas. Microtubules are marked with an antibody against tubulin (red); the nucleus is counterstained with DAPI (blue). The side of an image is 64 μm.

Peter J. Thul, et al.
Science 26 May 2017:
Vol. 356, Issue 6340, eaal3321
DOI: 10.1126/science.aal3321

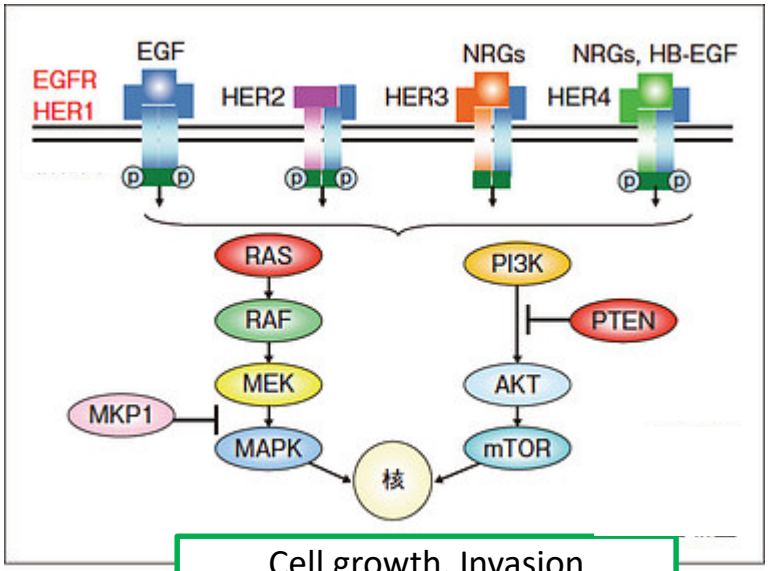


TRIM28 is highly expressed in many types of tumors (The Human Protein Atlas data). Immunohistochemistry was performed with rabbit polyclonal antibody HPA064033. Strong nuclear staining is observed in almost all types of cancers presented in The Human Protein Atlas database. Only lymphoma and liver and kidney tumors present medium intensity for TRIM28 staining. Normal tissues showed moderate to strong nuclear positivity with HPA064033 antibody as presented at the bottom, however in most cancer types the presence of TRIM28 in cancer cell nuclei is more pronounced than in adjacent normal tissues.

Czerwinska, P, et al. *J. Biomedical Science* (2017)

Molecular targeted therapies for cancer

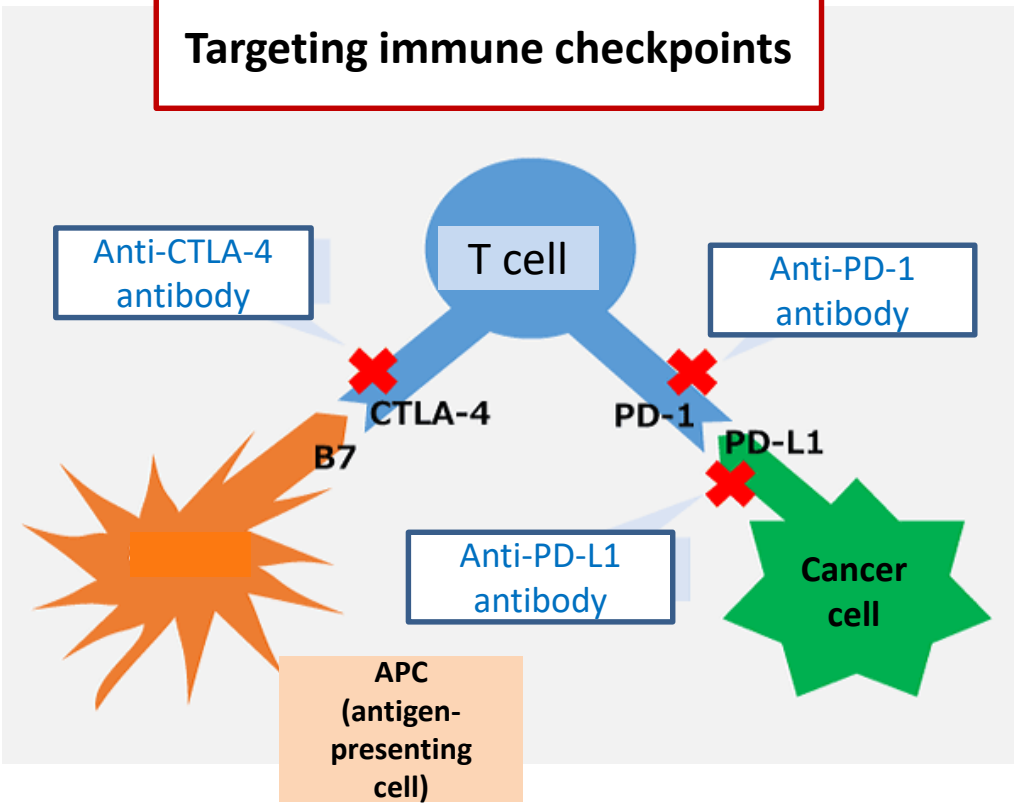
Targeting growth factors and their signaling molecules



Cell growth, Invasion
Metastasis, Angiogenesis

Responsible genes (responsible proteins) are targeted.

Targeting immune checkpoints



Protein-protein interaction (PPI) is targeted.

There are limitations to such molecular targeted therapy.

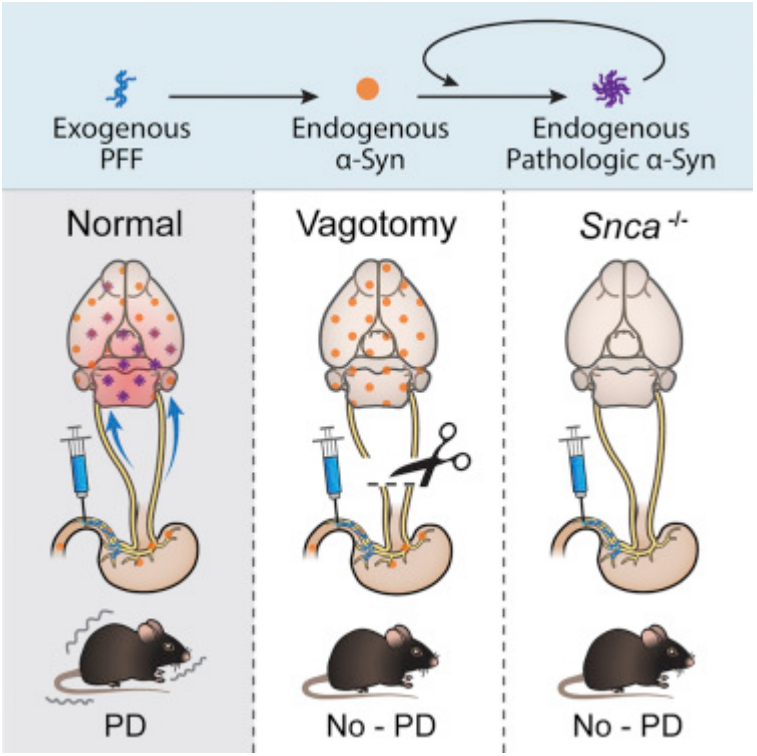
The rate of population aging in Japan is predicted to be kept significantly high. To achieve a prolonged and healthy life, “prevention or preventive intervention of diseases” is an important strategy. The burden of chronic diseases, such as diabetes and dementia, should be overcome.

We believe that conventional approach (that is, conventional molecular targeted therapy), where research focuses on a small number of contributing factors in specific organs, is not effective for intractable chronic disorders.

The human body is a network of mutually dependent organs and such chronic diseases are thought to be caused by dysfunction of the interactive network between the organs.

Now, there is a growing evidence of how these organs interact and function as a network.

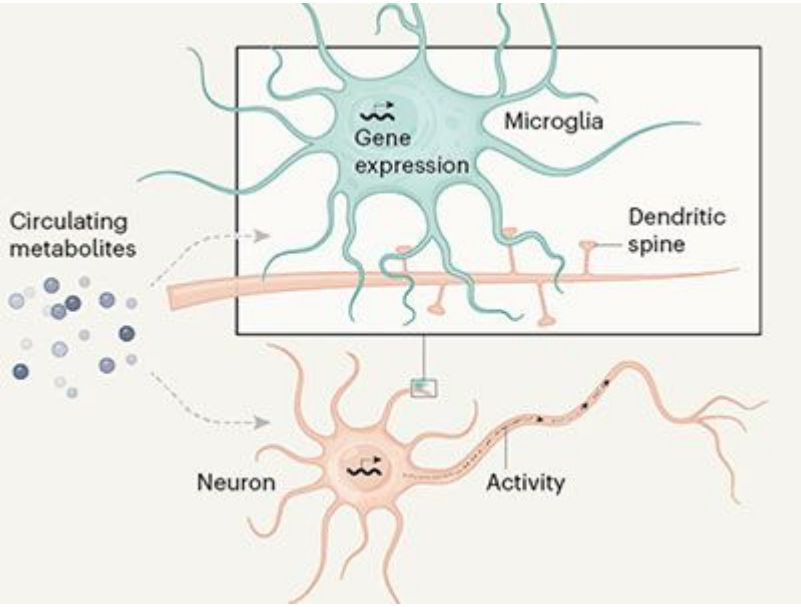
Transneuronal Propagation of Pathologic α-Synuclein from the Gut to the Brain Models Parkinson's Disease



- Gut-to-brain propagation of pathologic α-synuclein via the vagus nerve causes PD
- Dopamine neurons degenerate in the pathologic α-synuclein gut-to-brain propagation model of PD
- Gut injection of pathologic α-synuclein causes PD-like motor and non-motor symptoms
- PD-like pathology and symptoms require endogenous α-synuclein

Kim, S. et al. *Neuron*, Vol. 103: 627-641 (2019)

gut–brain communication

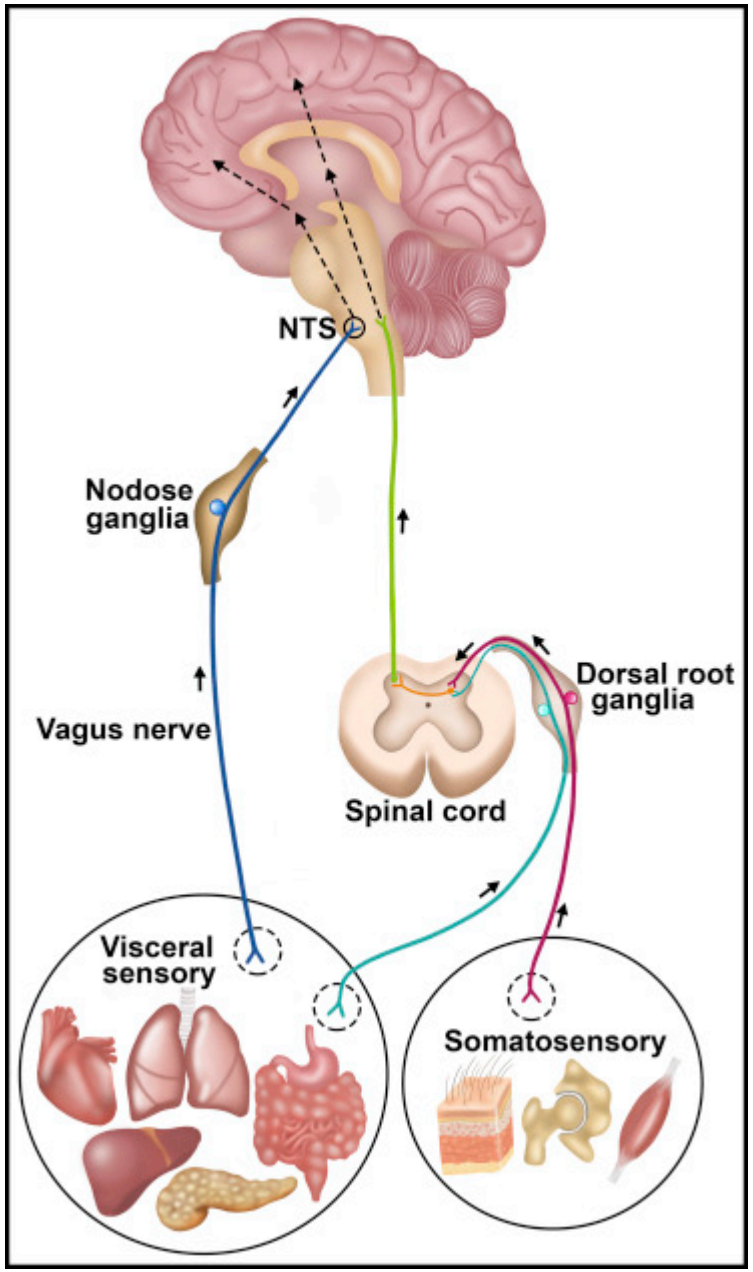


Gut microbes regulate neurons to help mice forget their fear

The gut's resident bacteria, the microbiota, can markedly affect the brain and behaviour. Chu *et al.* show that the microbiota is needed for mice to update their behaviour in response to changing environmental cues — for example, to stop reacting to a once-frightening stimulus when it is no longer threatening (a phenomenon called fear extinction). The authors hypothesize that this role in behavioural adaptation involves metabolite molecules that are produced by the microbiota and circulate in the blood. They suggest that the metabolites modulate the ability of the brain's immune cells, microglia, to engulf and degrade structures called dendritic spines that form synaptic connections between neurons. In addition, microglia could affect neuronal activity directly to promote behavioural adaptation. In support of this idea, they show that changes in the microbiota lead to altered gene expression in microglia and neurons, and to changes in dendritic-spine maintenance.

Drew D. Kiraly, Nature, Vol. 574: 488-489 (2019)

Neuro-immune Communication



Immune cell activation stimulates neuronal circuits that regulate innate and adaptive immunity. Molecular mechanistic insights into the inflammatory reflex and other neuro-immune interactions have greatly advanced our understanding of immunity and identified new therapeutic possibilities in inflammatory and autoimmune diseases. As reviewed by Chavan et al, recent successful clinical trials using bioelectronic devices that modulate the inflammatory reflex to significantly improve rheumatoid arthritis and inflammatory bowel disease provide a path for using electrons as a therapeutic modality for targeting molecular mechanisms of immunity. They also review mechanisms of peripheral sensory neuronal function in response to immune challenges, the neural regulation of immunity and inflammation, and the therapeutic implications of those mechanistic insights.

Chavan, S. S., et al. *Immunity* Vol. 46: 927-942 (2017)

In the future

Through the development of new biological and computational models, together with novel technologies for biosensing and imaging, important functional organ networks and their roles in the context of human life will be identified.

Thus, we can identify key factors, key pathways and key networks that switch on or off the system-level responses in the networks of organs, leading to the establishment of innovative prevention, diagnosis and novel intervention/treatment methods.

Thank you for your attention!