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18.09.21

Modelling Metabolomic changes in hBM-MSCs during Osteogenic Differentiation

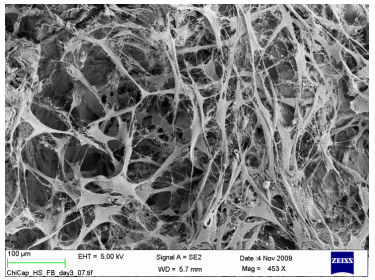
PART OF THE CURRICULUM IN HEMATOLOGY O1 – HERO PROJECT SEE 2014-2021 NO. 19-COP-0031

HE-RO-IS STRATEGIC COOPERATION IN HEMATOLOGY

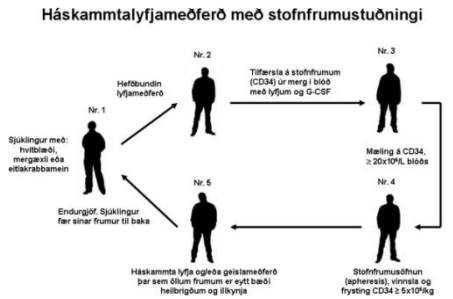
Profesor Olafur E. Sigurjonsson, Reykjavik University
The Blood bank – Landspitali University Hospital

HÁSKÓLINN Í REYKJAVÍK REYKJAVÍK UNIVERSITY

BLÓÐBANKINN

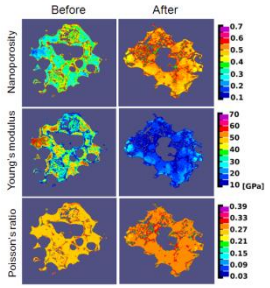


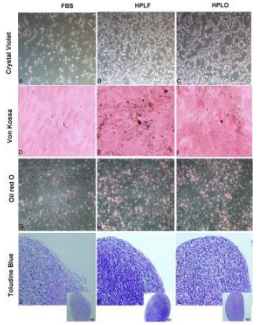
Clinical use of sem cells
Hematopoietic stem cells
ISO9001/JAICE



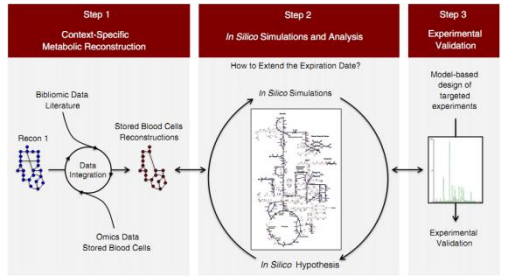
Tissue engineering
Bone and cartilage

Transfusion medicine
Systems biology





Stem cells
Development of GMP cell culture




Archaeomics
Epigenomics
Morphomics
Regulomics
Toxicogenomics
Phosphoproteomics
Metabolomics
Kinomics
Alternatomics
Glycomics
Lipoproteomics
Secretomics
Proteomics
Behavioromics
Genomics
Transcriptomics
Lipidomics
Fluxomics
Interactomics
Orfeomics

Purpose

- Can be split into 3 categories

- **To identify temporal changes** in metabolic activity of mesenchymal stem cells during the course of OD through analysis of metabolomic and transcriptomic data to see if the progression can be split up into different phases, each with its own identifying metabotype.
- **To reconstruct an original** and hitherto unseen trio of comparable genome scale metabolic models, modelling metabolism of mesenchymal stem cells during the first seven days of OD and AD as well as proliferation.
- **To bring together the possibilities** that lie within the fields of genome scale metabolic modelling, metabolomics and stem cell-based medicine and highlight how they can all can be combined in order to further the use of mesenchymal stem cells in tissue engineering and regenerative medicine.

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Mesenchmal stem cells

The promise that they hold

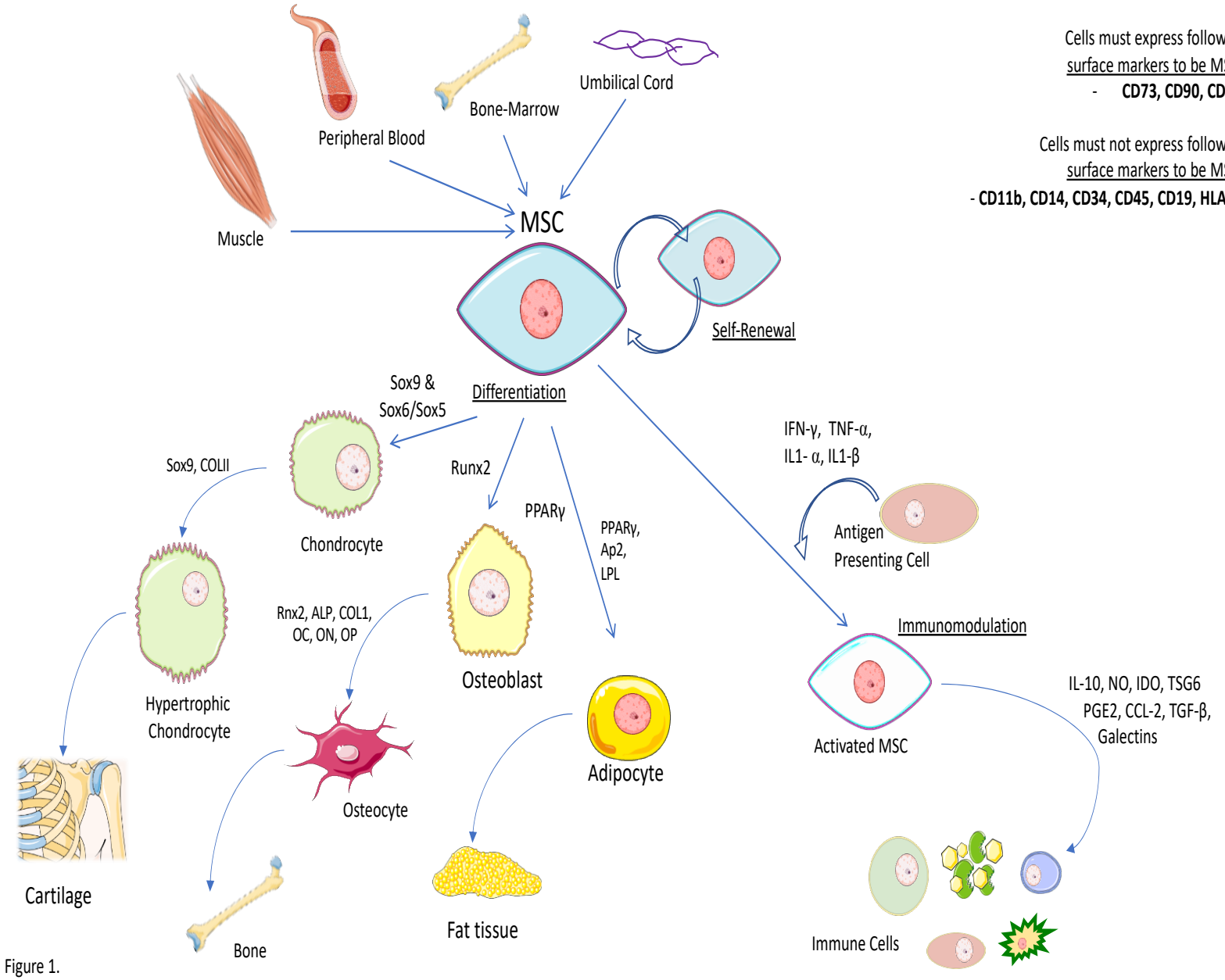


Figure 1.

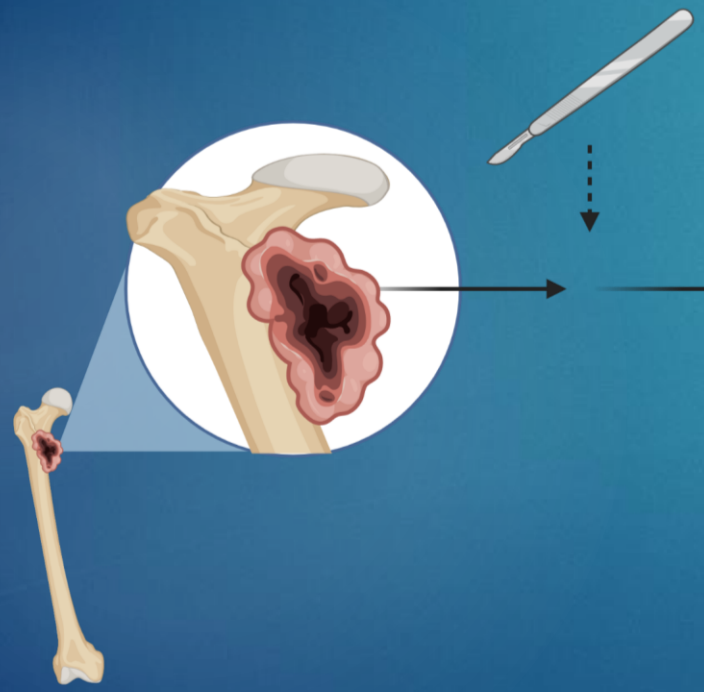
Cells must express following surface markers to be MSCs:

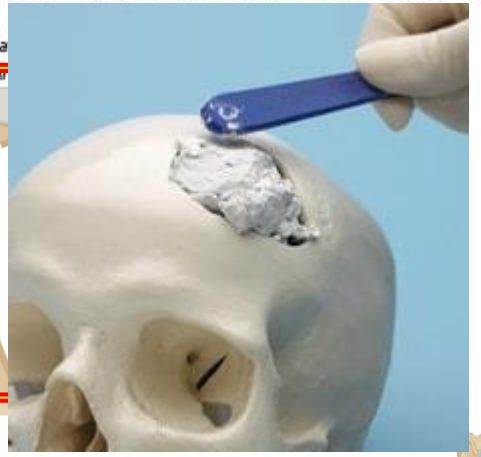
- **CD73, CD90, CD105**

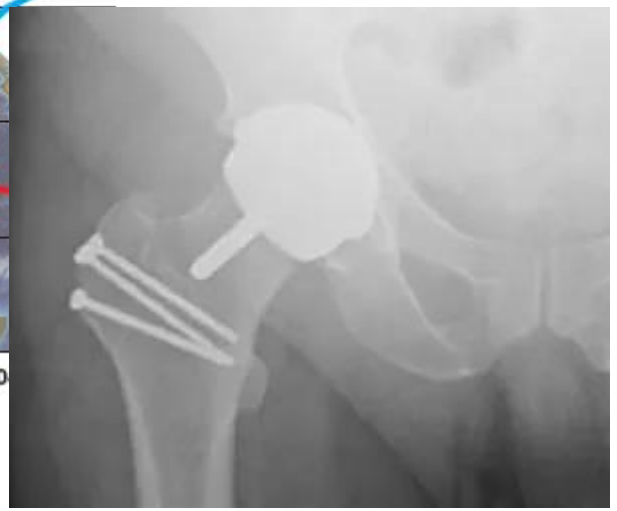
Cells must not express following surface markers to be MSCs:

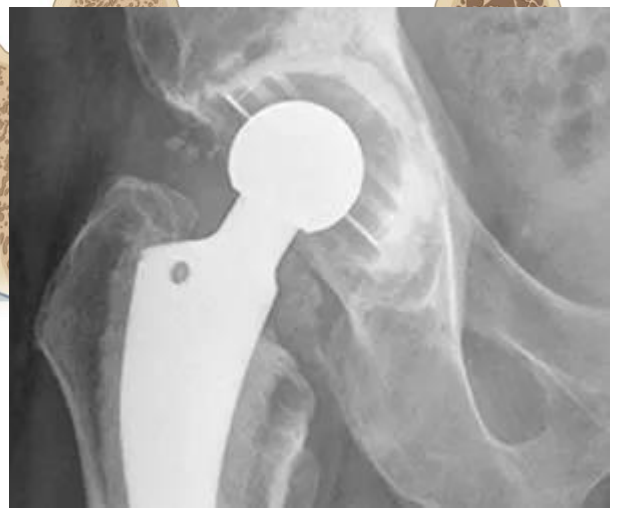
- **CD11b, CD14, CD34, CD45, CD19, HLA-DR**

Ostegenesis



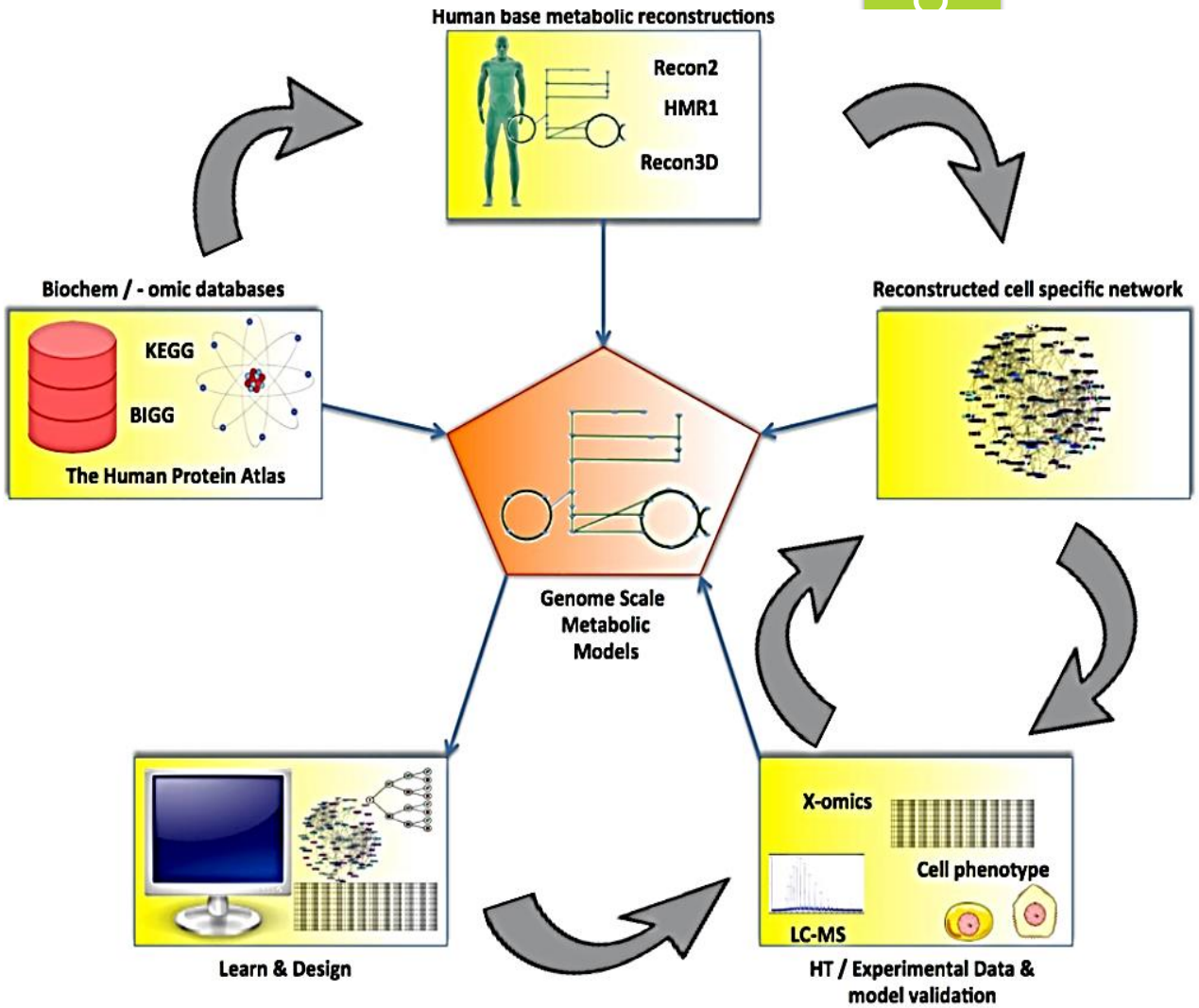






What value do GEMs bring to this project?

- Multiple components and variables need to be accounted for *at the same time.*
- Only way to get a holistic picture
- GEMs combine genomic and bibliomic data to represent biochemical, genetic and genomic (BiGG) base that is converted into a mathematical format
- Allow for integration of HT multi – omic data, enabling creation of context specific models capable of making more accurate predictions.



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doi: 10.21037/atm-20-3140

PMCID: PMC7859772
PMID: 33553361

A narrative review of central nervous system involvement in acute leukemias

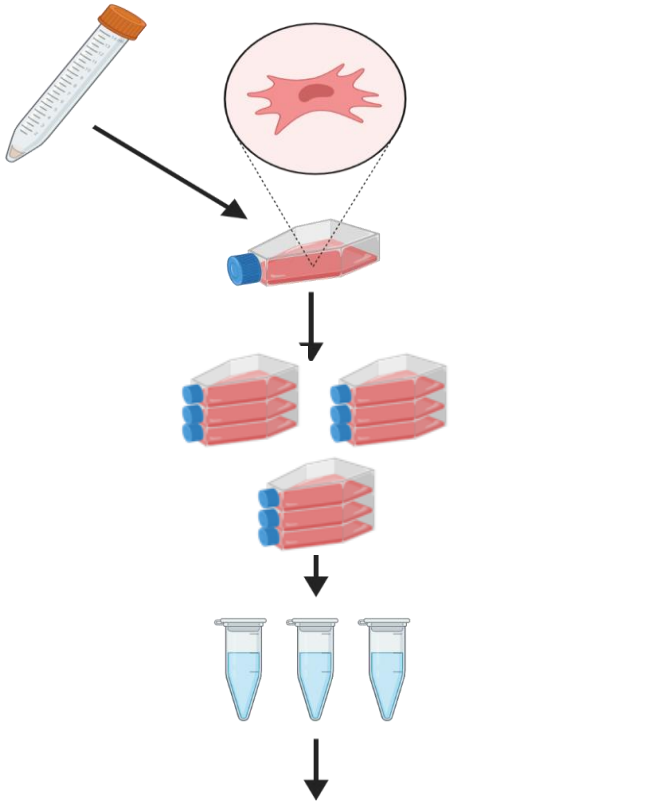
Dalma Deak,[1,2,#] Nicolae Gorcea-Andronic,[2,#] Valentina Sas,[2,3] Patric Teodorescu,[1,2] Catalin Constantinescu,[2,4] Sabina Iluta,[1,2] Sergiu Pasca,[1,2] Ionut Hotea,[1,2] Cristina Turcas,[1,2] Vlad Moisoiu,[5] Alina-Andreea Zimta,[6] Simona Galdean,[1] Jakob Steinheber,[2] Ioana Rus,[1] Sebastian Rauch,[2] Cedric Richlitzki,[2] Raluca Munteanu,[6] Ancuta Jurj,[7] Bobe Petrushev,[6] Cristina Selicean,[1] Mirela Marian,[1] Olga Soritau,[1] Alexandra Andries,[8] Andrei Roman,[8,9] Delia Dima,[1] Alina Tanase,[10] Olafur Sigurjonsson,[11] and Ciprian Tomuleasa[✉1,2,6]

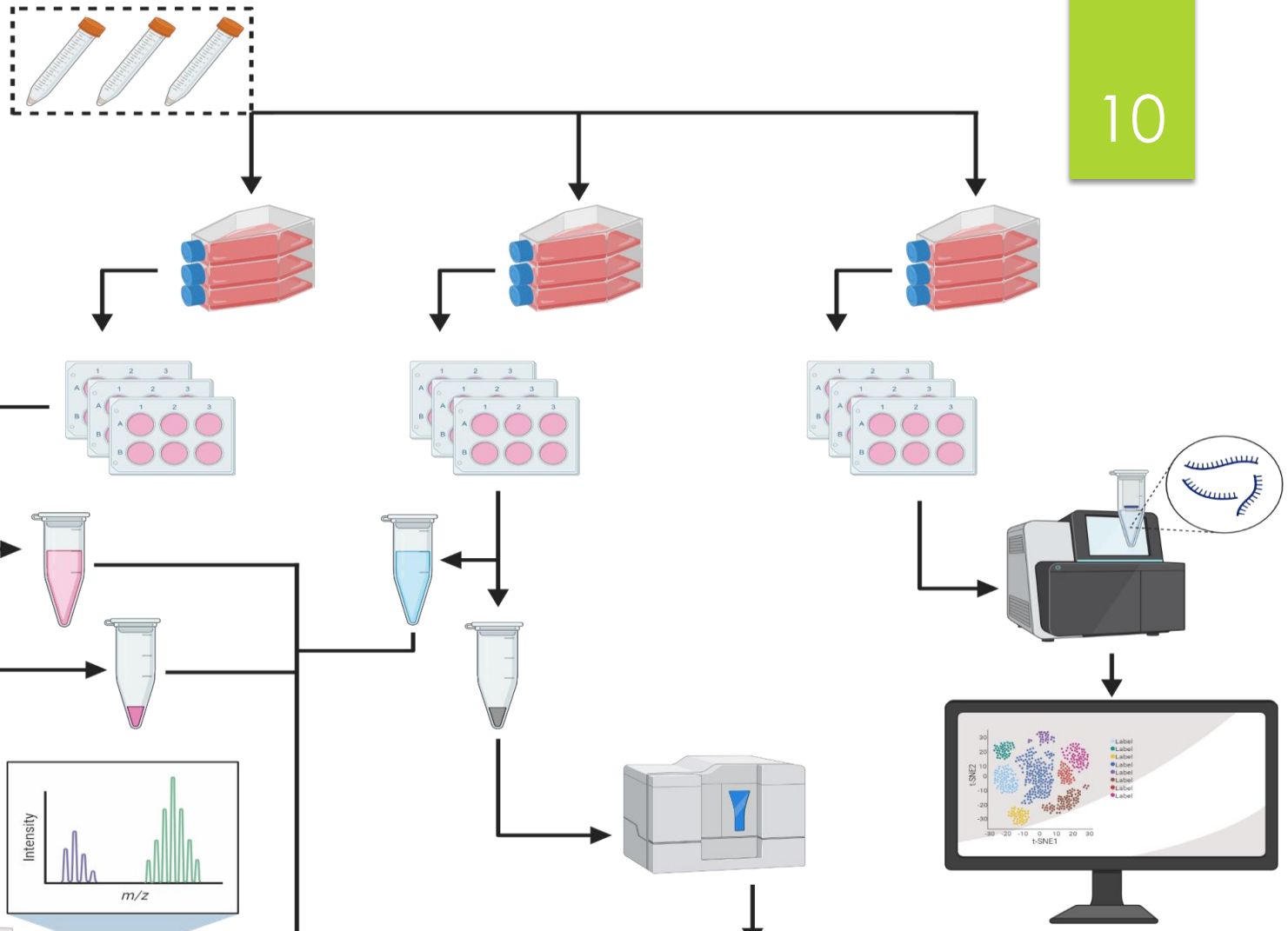
Abstract

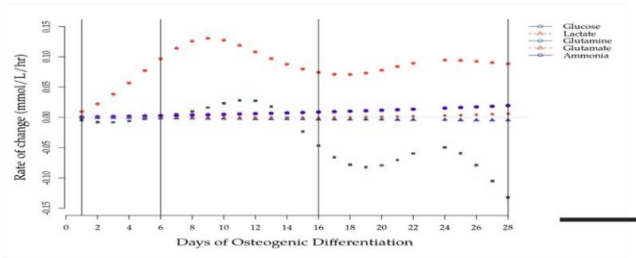
Go to: ▸

Acute leukemias (both myeloid and lymphoblastic) are a group of diseases for which each year more successful therapies are implemented. However, in a subset of cases the overall survival (OS) is still exceptionally low due to the infiltration of leukemic cells in the central nervous system (CNS) and the subsequent formation of brain tumors. The CNS involvement is more common in acute lymphocytic leukemia (ALL), than in adult acute myeloid leukemia (AML), although the rates for the second case might be underestimated. The main reasons for CNS invasion are related to the

Story #1




Intensity
m/z
Title
t-SNE2
t-SNE1


Rate of change (mmol/L/hr)
Days of Osteogenic Differentiation
Glucose
Lactate
Glutamine
Glutamate
Ammonia

Continuous renal replacement therapy in cytokine release syndrome following immunotherapy or cellular therapies?

Catalin Constantinescu [1 2], Sergiu Pasca [1 3], Tiberiu Tat [4], Patric Teodorescu [1 4], Catalin Vlad [5], Sabina Iluta [1 4], Delia Dima [4], Dana Tomescu [6 7], Ecaterina Scarlatescu [8], Alina Tanase [8], Olafur Eysteinn Sigurjonsson [9 10], Anca Colita [8], Hermann Einsele [11], Ciprian Tomuleasa [12]

Affiliations + expand

PMID: 32474415 PMCID: PMC7264828 DOI: 10.1136/jitc-2020-000742

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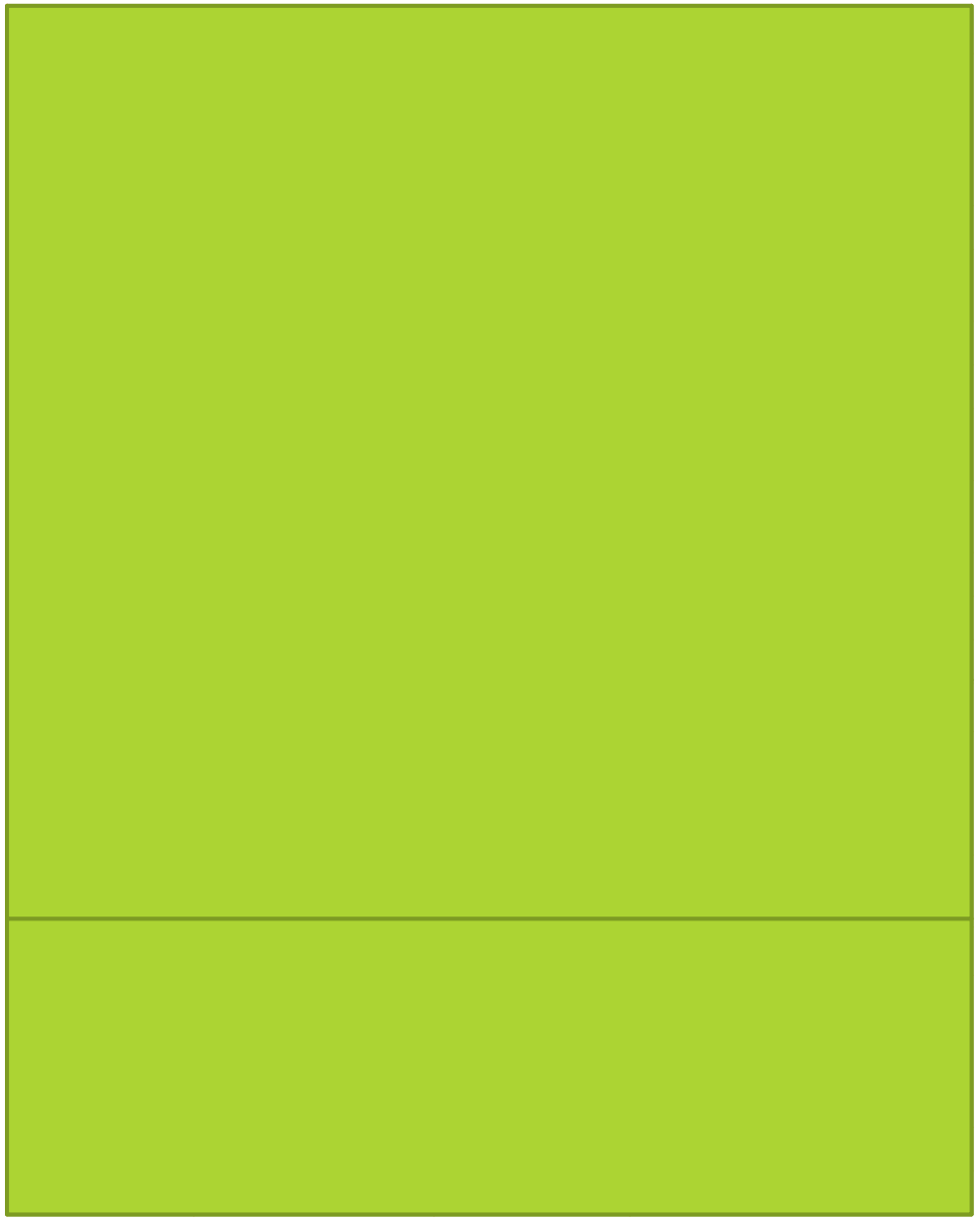
Abstract

Recently, an increasing number of novel drugs were approved in oncology and hematology. Nevertheless, pharmacology progress comes with a variety of side effects, of which cytokine release syndrome (CRS) is a potential complication of some immunotherapies that can lead to multiorgan failure if not diagnosed and treated accordingly. CRS generally occurs with therapies that lead to highly activated T cells, like chimeric antigen receptor T cells or in the case of bispecific T-cell engaging antibodies. This, in turn, leads to a proinflammatory state with subsequent organ damage. To better manage CRS there is a need for specific therapies or to repurpose strategies that are already known to be useful in similar situations. Current management strategies for CRS are represented by anticytokine directed therapies and corticosteroids. Based on its pathophysiology and the resemblance of CRS to sepsis and septic shock, as well as based on the principles of initiation of

Story #2



Exchange/demand reactions
Extracellular Space
Cell Membrane
Glucose
Cytosol
Exchange / Demand reactions
Extracellular Space
Cell Membrane
Exchange / Demand reactions
Extracellular Space
Cell Membrane
Cytosol
Glucose
Glycolysis
Glucose
Lysosomal Transport
Lactate
Pyruvate
PPP
ROH
Vitamin A/ RE
Cofactor
Cofactor
Biotin
Active vitamin form
Ribulose 5-phosphate
Lipogenesis
Mitochondrial transport
Pyruvate
Fatty Acid
Acetyl CoA
Fatty Acid Synthesis
Oxaloacetate
Citrate
Cholestrol Metabolism
TCA
Acetyl CoA
β-Fatty Acid Oxidation
Fumarate
Succinyl CoA
Oxidative Phosphorylation
Sphingolipid Metabolism
Fatty Acid
18.09.21
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HE-RO-IS
strategic cooperation in hematology – HERO

Iceland Liechtenstein Norway grants

"Working together for
a green, competitive and inclusive Europe"

Papers published in cooperation during HERO SEE

- •Zimta AA, Sigurjonsson OE, Gulei D, Tomuleasa C. The Malignant Role of Exosomes as Nanocarriers of Rare RNA Species. Int J Mol Sci. 2020 Aug 15;21(16):5866.
- •Catalin Constantinescu, Sergiu Pasca, Alina-Andreea Zimta , Tiberiu Tat , Ioana Rus , Patric Teodorescu , Sabina Iluta , Alina Tanase , Anca Colita , Olafur Sigurjonsson , Hermann Einsele , Ciprian Tomuleasa Overview of the Side-Effects of FDA- and/or EMA-Approved Targeted Therapies for the Treatment of Hematological Malignancies. J Clin Med. 2020 Sep 8;9(9):2903.Only proliferation → Asparagine, Folate, Fumarate
- •Minodora Desmirean , Sebastian Rauch , Ancuta Jurj , Sergiu Pasca , Sabina Iluta , Patric Teodorescu , Cristian Berce , Alina-Andreea Zimta , Cristina Turcas , Adrian-Bogdan Tigu , Cristian Moldovan , Irene Paris , Jakob Steinheber , Cedric Richlitzki , Catalin Constantinescu , Olafur Eysteinn Sigurjonsson , Delia Dima , Bobe Petrushev, Ciprian Tomuleasa . B Cells versus T Cells in the Tumor Microenvironment of Malignant Lymphomas. Are the Lymphocytes Playing the Roles of Muhammad Ali versus George Foreman in Zaire 1974? J Clin Med. 2020 Oct 24;9(11):3412.
- •Catalin Constantinescu, Sergiu Pasca, Tiberiu Tat, Patric Teodorescu, Catalin Vlad, Sabina Iluta, Delia Dima, Dana Tomescu, Ecaterina Scarlatescu, Alina Tanase, Olafur Eysteinn Sigurjonsson, Anca Colita, Hermann Einsele, Ciprian Tomuleasa. Continuous renal replacement therapy in cytokine release syndrome following immunotherapy or cellular therapies? J Immunother Cancer. 2020 May;8(1):e000742.
- •Deak D, Gorcea-Andronic N, Sas V, Teodorescu P, Constantinescu C, Iluta S, Pasca S, Hotea I, Turcas C, Moisoiu V, Zimta AA, Galdean S, Steinheber J, Rus I, Rauch S, Richlitzki C, Munteanu R, Jurj A, Petrushev B, Selicean C, Marian M, Soritau O, Andries A, Roman A, Dima D, Tanase A, Sigurjonsson O, Tomuleasa C. A narrative review of central nervous system involvement in acute leukemias. Ann Transl Med. 2021 Jan;9(1):68. doi: 10.21037/atm-20-3140.

Review > J Clin Med. 2020 Oct 24;9(11):3412. doi: 10.3390/jcm9113412.

B Cells versus T Cells in the Tumor Microenvironment of Malignant Lymphomas. Are the Lymphocytes Playing the Roles of Muhammad Ali versus George Foreman in Zaire 1974?

Minodora Desmirean [1 2], Sebastian Rauch [1], Ancuta Jurj [1], Sergiu Pasca [1], Sabina Iluta [1], Patric Teodorescu [1], Cristian Berce [3], Alina-Andreea Zimta [3], Cristina Turcas [1], Adrian-Bogdan Tigu [3], Cristian Moldovan [3], Irene Paris [2], Jakob Steinheber [1], Cedric Richlitzki [1], Catalin Constantinescu [1 4], Olafur Eysteinn Sigurjonsson [5 6], Delia Dima [7], Bobe Petrushev [3 8], Ciprian Tomuleasa [1 7]

Affiliations + expand

PMID: 33114418 PMCID: PMC7693982 DOI: 10.3390/jcm9113412

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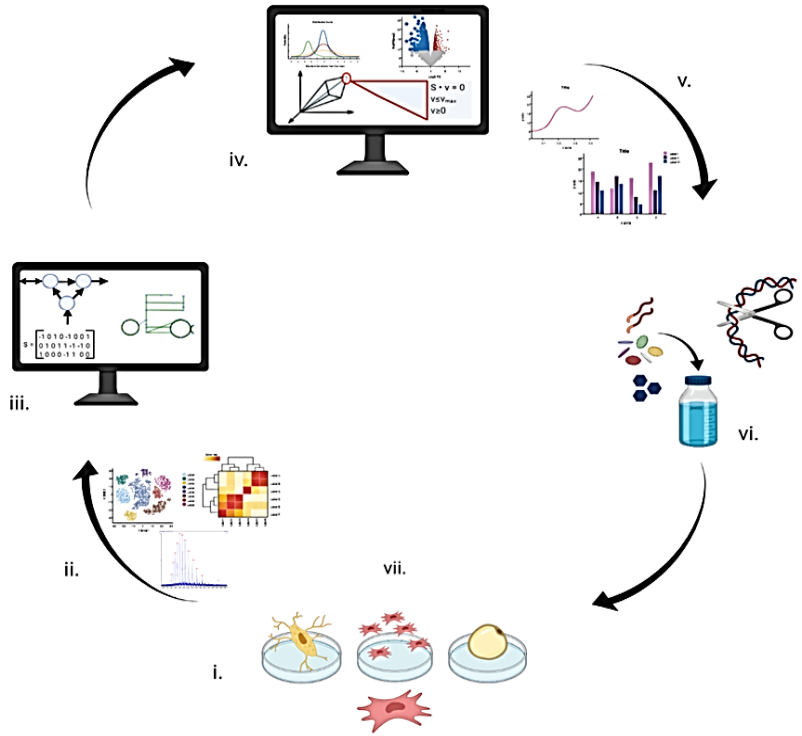
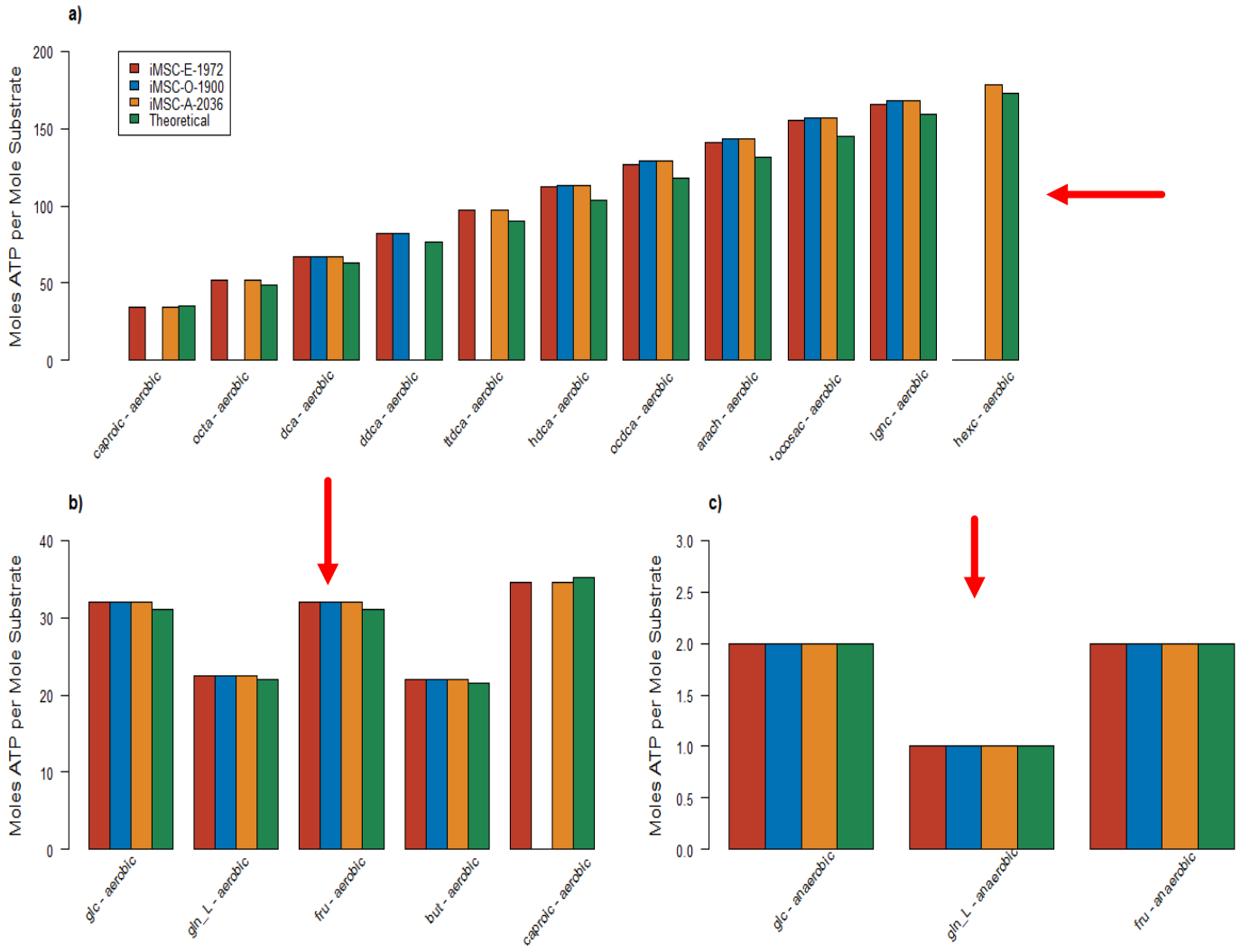


Newly reconstructed models expand coverage of metabolic pathways and accurately represent core metabolic fluxes.



Model comparison (both internal and the iMSC1255 model):

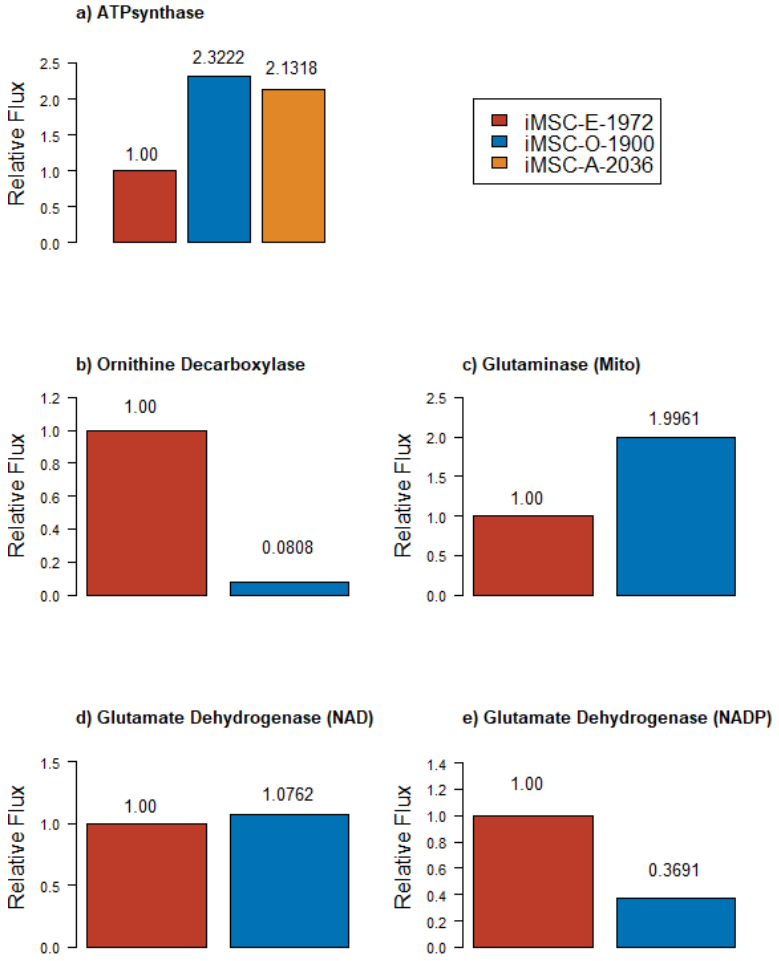
- Could recapitulate known differences between cell lineages
- Expanded coverage of metabolic pathways (to iMSC1255)
- Accurate representation of core metabolic fluxes.

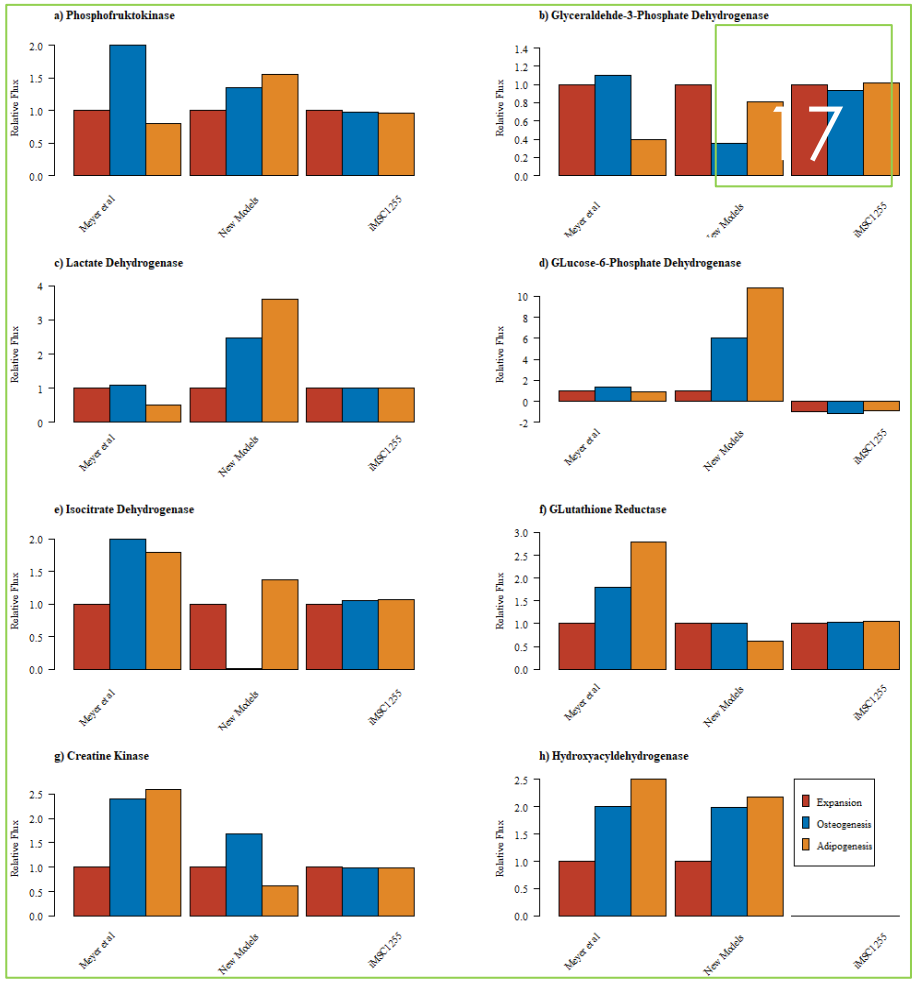
Near correct ATP production (glucose/glutamine):

- Glucose:
  - A = 32 molecules
  - Ana = 2 molecules
- Glutamine
  - A = 23
  - Ana = 2

Comparison of yield between reconstructions and theoretical values:

- (A) Aerobic metabolism of the most energy dense substrates
- (B) Aerobic metabolism of the least energy dense substrates
- (C) Anaerobic metabolism





Mitochondrial Function Separates Proliferating and Differentiating MSCs and Pentose Phosphate Pathway Flux Differentiates Osteogenesis and Adipogenesis