



**Islets for US**  
Collaborative

**We ask the Advisory Committee to recommend against approval of BLA 125734 for donislecel (purified allogeneic deceased donor pancreas derived Islets of Langerhans)**

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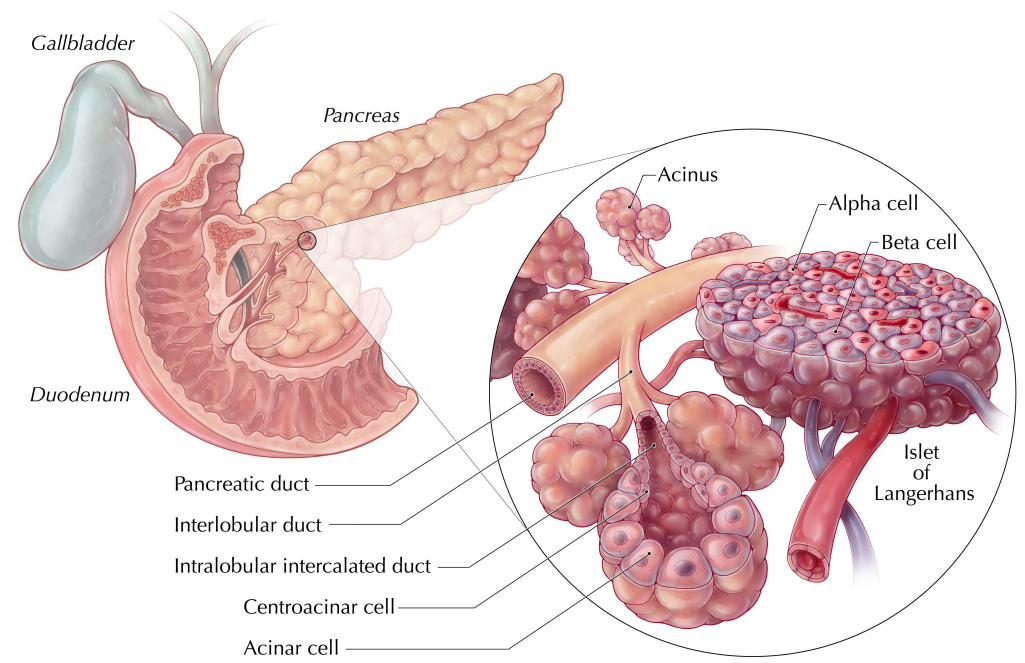
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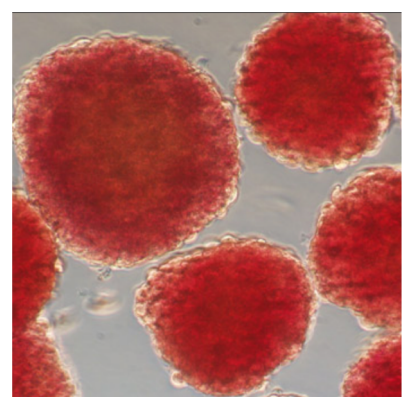
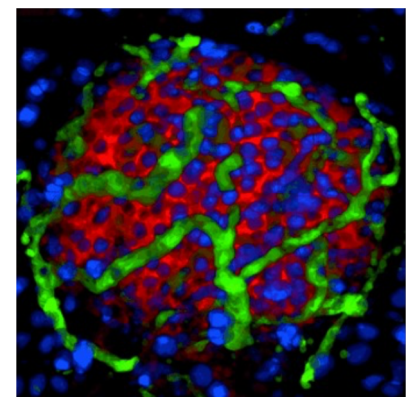
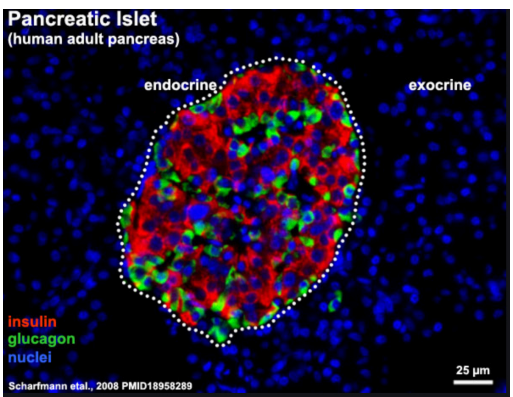
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- Islets are human micro-organs and should be regulated consistent with pancreas and other human organs, which are regulated by FDA, and for which BLA is not required
- Islets are not drugs, and are not a type of cell therapy,



Islets as any other organ for transplantation:

- are built from many different type of cells with very well- integrated function
- have own internal blood vessel and neural network
- maintain own morphology and structure during processing and after transplantation
- connect own vasculature to the recipient blood vessel network after the transplantation
- cannot be frozen
- can be only preserved for short period of time
- require constant supervision by the transplant team starting from the moment of donor selection through pancreas recovery, processing and preservation, transplantation and finally post-transplant patient care in order to reassure safety, effectiveness and appropriate clinical outcome of the transplant procedure



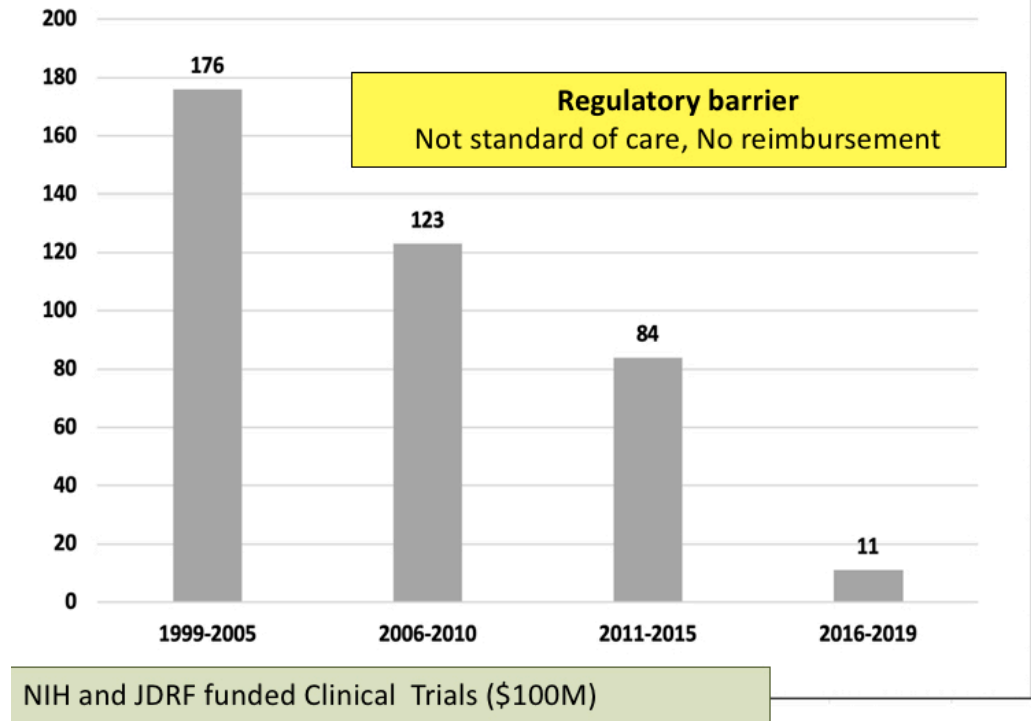
# 1. FDA's position that allogeneic islets require a BLA has prevented the procedure from becoming standard of care in the U.S., in contrast to many other countries

## Academic transplant centers

- processed human islets for transplantation successfully without BLA in clinical trials over last 20 years
- are not drug manufactures, are in position to sponsor the BLA or comply with other FDA's drug manufacturing requirements
- have a different mission
  - lack of appropriate organizational structure and resources
  - unable to meet financial and legal BLA demands

Consequently, after 20 years of research, islets transplantation still cannot be broadly available to Americans with Type 1 Diabetes

**Catastrophic decline in the number of new patients treated with islet transplantation in the US**



**In contrast, many countries in Europe, Canada, Australia and Japan**

- regulate islets as organs for transplantation
- have already implemented islet transplantation as a standard of care procedure
- directly benefited from:
  - US islet isolation and transplantation technology developed through federally funded research (\$100M)

## 2. Granting a BLA to a private, for-profit company, **will not solve the problem** of islet transplantation in the US but it will **lead to its further demise**

Once the BLA is approved, **a for-profit entity will have**

- a right to commercialize human islets as a biological drug for use in transplantation
  - This is inconsistent with the federal prohibition on commercialization of human organs
- 7 years of marketing exclusivity under the Orphan Drug Act,
- a significant leverage in the terms of **the contract** with every transplant center, including **the price for the islets**
- a significant influence over which transplant centers are able to offer their patients islet transplants

**As a consequence**

- Transplant centers will have no alternative source of islets for clinical use
- Transplant centers will have less control over the quality of islets for their patients
- Access to islet transplantation might be reduced because of cost and limited availability of islets

### 3. Granting a BLA **will compromise patient safety**

- The Health Resources and Services Administration (HRSA) developed regulations to ensure the safe and ethical allocation and transplantation of **human organs**
- Under HRSA, Organ Procurement and Transplantation Network (OPTN) and United Network for Organ Sharing (UNOS) oversees transplant programs that provide complex medical therapy through a multidisciplinary team of transplant physicians.
- UNOS/OPTN oversight framework is critical to reassure patients safety and effectiveness of this very complex transplant therapy which extends beyond the transplant procedure.
- **As a result of the BLA requirement, islets will NOT be included into the complete OPTN/UNOS oversight**
  - **the commercial BLA-holder, and patients after islet transplantation, will not be subject to OPTN/UNOS post-transplant monitoring of patient outcomes**
  - Islets will be LESS regulated than all other human organs
- **Regulating islets as drugs subject to a BLA results in removal of the critical safeguards applied by OPTN/UNOS, which will jeopardize the safety of our patients**

## 4. Solution

Human islets should be regulated as organs under HRSA through OPTN and UNOS, not as drugs by FDA

- Congress included **human organ subparts into the NOTA's definition** of human organ in the amendment in 1988, which applies to islets as subparts of the pancreas (42 USC § 274e(c)(1) amended in 1988), **but**
- the definition of human organ under the **OPTN Final Rule has not been amended** to include human islets.
- consequently, for the past 20 years, FDA has taken the position that islets are a biological drug requiring premarket approval of a biologics license application.

## 4. Solution

The Secretary of HHS should designate allogeneic islets for transplantation as human organs under the OPTN Final Rule.

1. Legally, it would conform with the statutory definition of the human organ under the National Organ Transplantation Act (NOTA).
2. Providing OPTN/UNOS with legal authority for holistic, systematic clinical oversight over islet transplantation would protect patients by ensuring the safety and effectiveness of islet transplantation therapy.
3. It would prevent imminent commercialization of human islets, which is prohibited under NOTA, by preventing the FDA from granting a biologics license application (BLA) for human islets to a commercial entity.
4. HHS' decision in 2013 to include vascularized composite allografts (VCAs) under OPTN/UNOS jurisdiction provides a strong precedent for including human islets under the OPTN final rule.
5. It would **not compromise** islet processing regulatory oversight, which could remain subject to **FDA Good Tissue Practice (GTP)** requirements as currently is the case for **islets for autologous use processed in the same manner as islets for allogeneic use.**



FDA's position that a BLA is required for unrelated allogeneic islets is inconsistent with the agency's approach to first and autologous islets

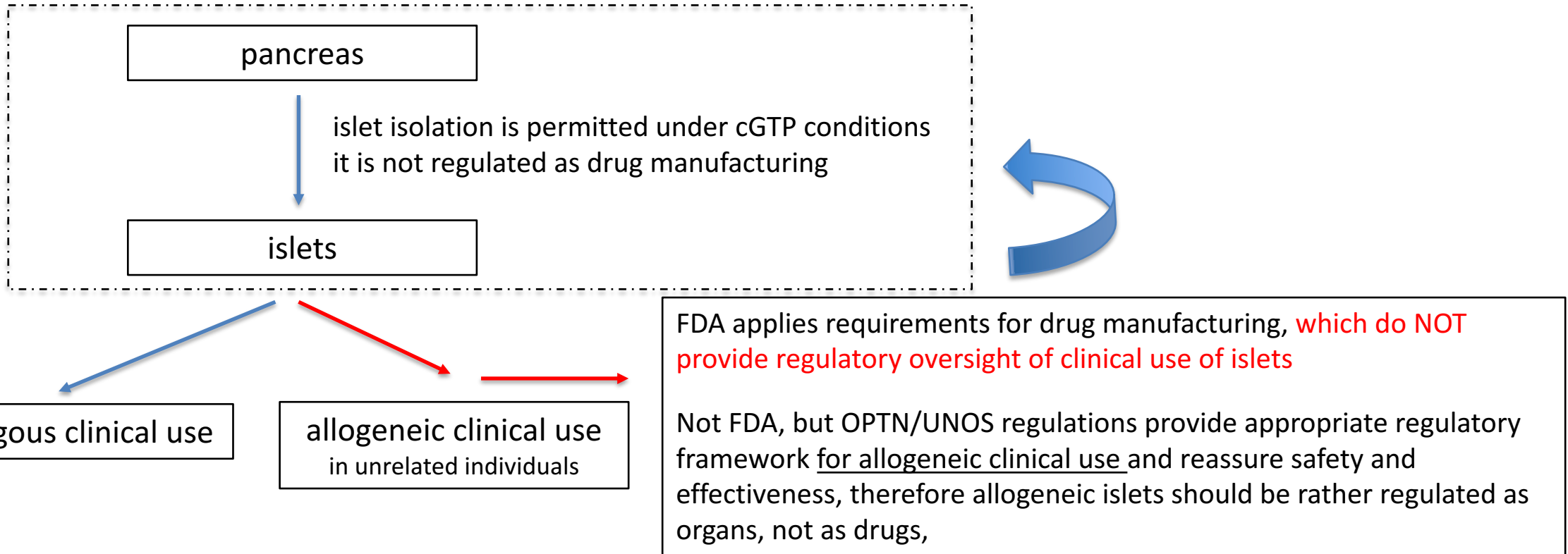
If islets are for use in the same person (autologous use)- no BLA is needed, and no drug manufacturing conditions required (just GTP)

If islets are for use in the first-/second degree relatives (allogeneic use)- no BLA is needed, no drug manufacturing conditions required (GTP)

If islets are for use between unrelated people (allogeneic use)- **BLA is required and drug related regulations (GMP)**

The same islet isolation technique is needed for allogeneic and autologous islets, but only allogeneic islets require a BLA  
FDA is disadvantaging patients who need unrelated allogeneic islets without an apparent safety rationale for imposing drug manufacturing standards

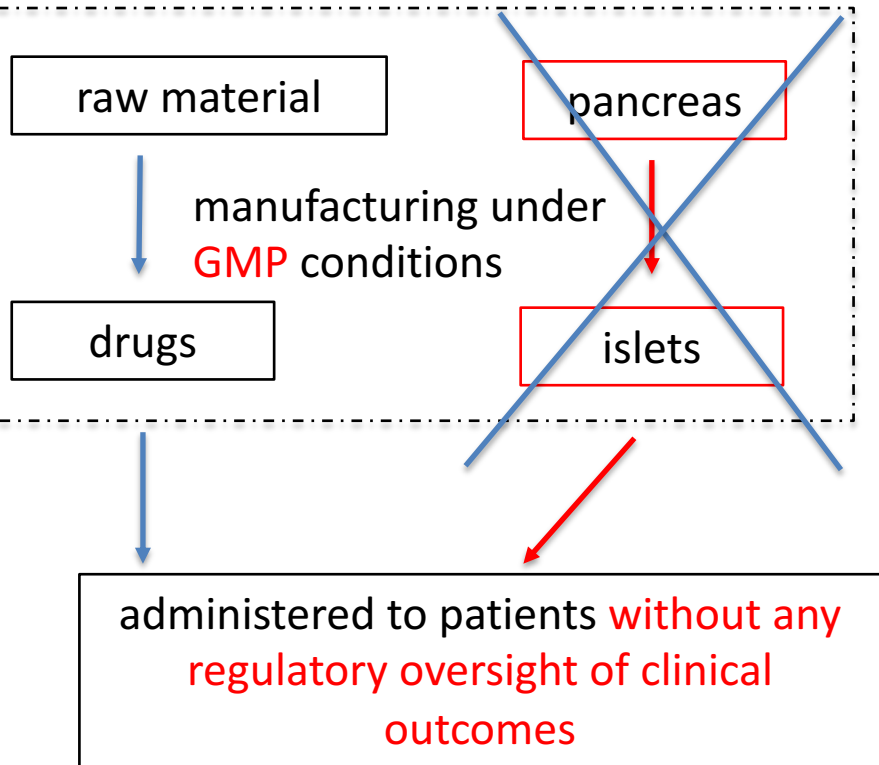
### FDA oversight of islet processing



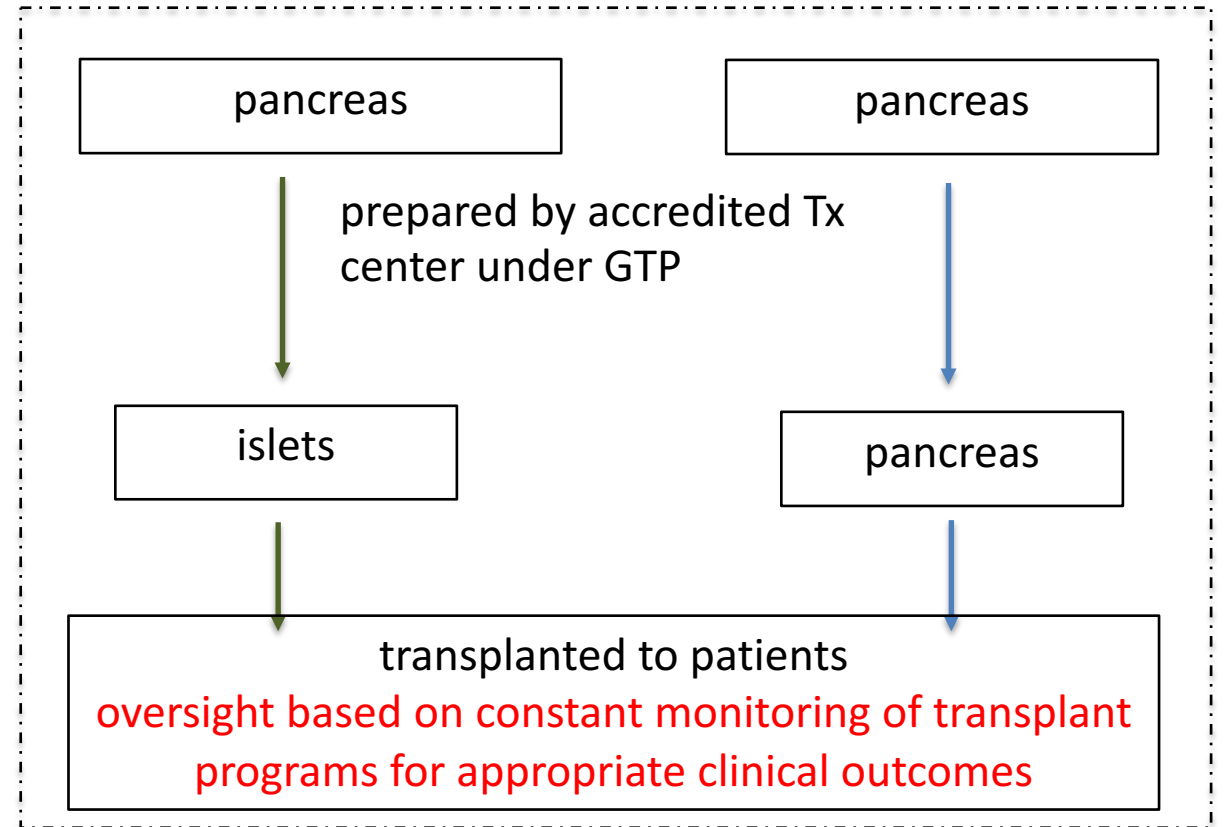
Safety and effectiveness of islets for allogeneic clinical use can be assured only by regulating them as human organs subject to OPTN/UNOS oversight

Such system will allow academic centers to continue process and transplant the islets, which lead to healthy competition stimulating progress in the field and access to the procedure for the patients.

### FDA oversight of drug production



### HRSA OPTN/UNOS oversight





- BLA 125734 raises significant legal, policy, and public health considerations that should be properly addressed by the Secretary of HHS and, if necessary, the Congress
- We are concerned that the Advisory Committee may have not been aware of the adverse, potentially irreversible consequences to patient safety and access of a recommendation to approve the BLA
- We therefore ask the Advisory Committee to recommend against approval of BLA 125734 for donislecel (purified allogeneic deceased donor pancreas derived Islets of Langerhans)

Thank you very much

Supplementary materials:

1. Letter to the Secretary of HHS Xavier Becerra sent on March 25<sup>th</sup>, 2021.
2. Witkowski P, Barth RN, Japour AJ, et al. on behalf of the “Islet for US Collaborative”. Regulatory updates are needed to prevent the commercialization of islet transplantation in the US. *Am J Transplant*, 2021, March 8, <https://doi.org/10.1111/ajt.16555>.
3. Witkowski P, Philipson L, Kaufman DB, et al. The “Islets for US” Collaborative. The Demise of Islet Allotransplantation in the US: A Call for an Urgent Regulatory Update. *Am J Transplant*, 2020, Nov 29, doi:10.1111/ajt.16397.
4. Weir GC, S. Bonner-Weir S. Why pancreatic islets should be regarded and regulated like organs. *CellR4* 2021; 9: e3083.
5. Abdulreda MH, Berggren PO. The pancreatic islet: a micro-organ in control. *CellR4* 2021; 9: e3093.