CELL THERAPY FOR NEUROLOGICAL DISEASE

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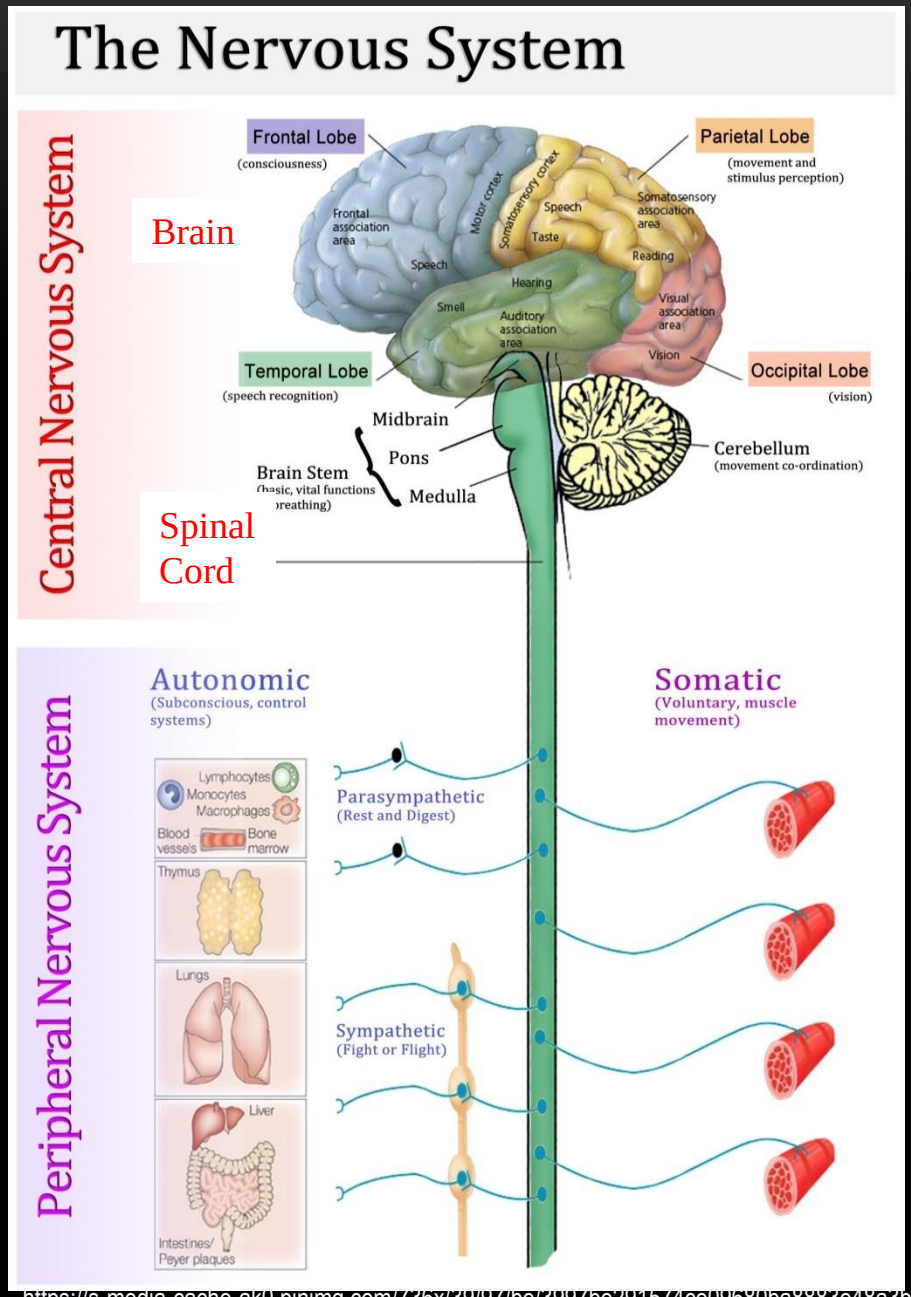
UNMET MEDICAL NEED



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Disease
Approx prevalance

Alzheimer's 5.3MM

Parkinson's 0.5MM

Stroke 7MM

Psychiatric Disease 1 in 4

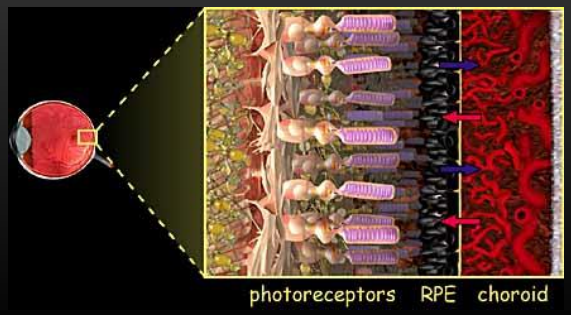
Multiple Sclerosis 2.3MM

ALS 20,000

Spinal Cord Injury 300,000

Peripheral nerve injury/neuropathy 20MM

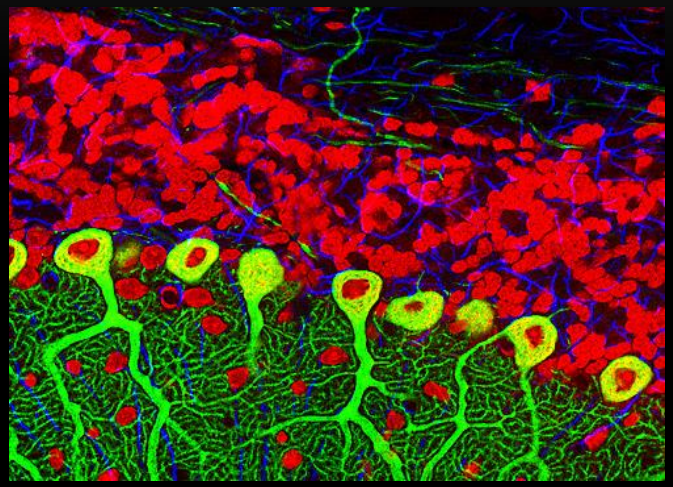
Retina

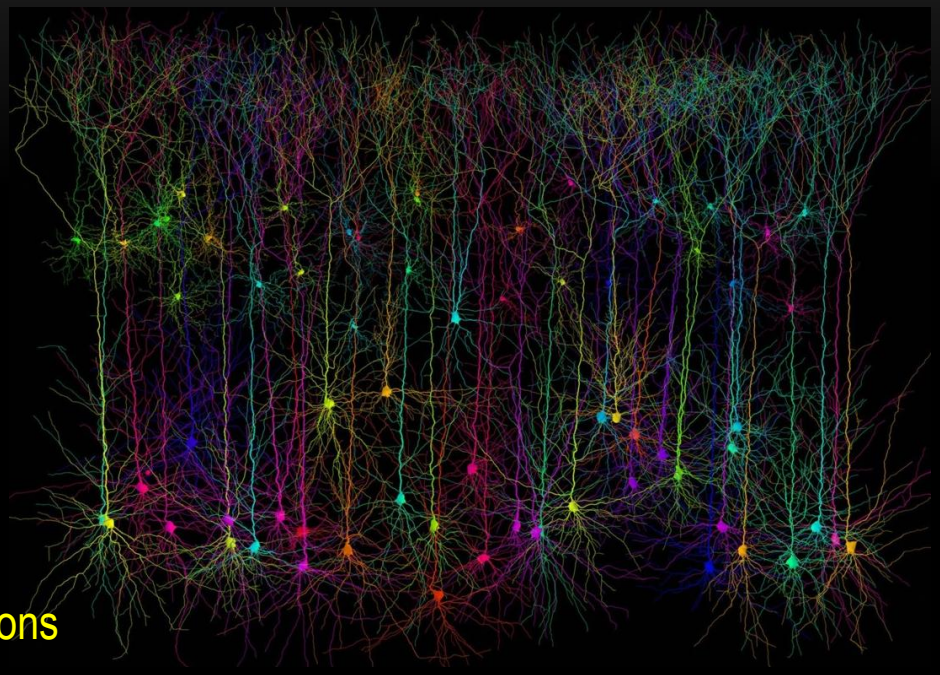


Age-related Macular Degeneration 10MM

+ Traumatic Injury

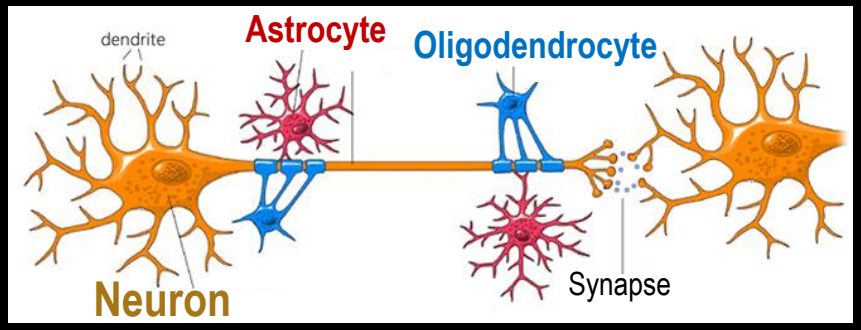
EVERY NEURAL REGION HAS UNIQUE CELL TYPES AND COMPLEX INTERACTIONS

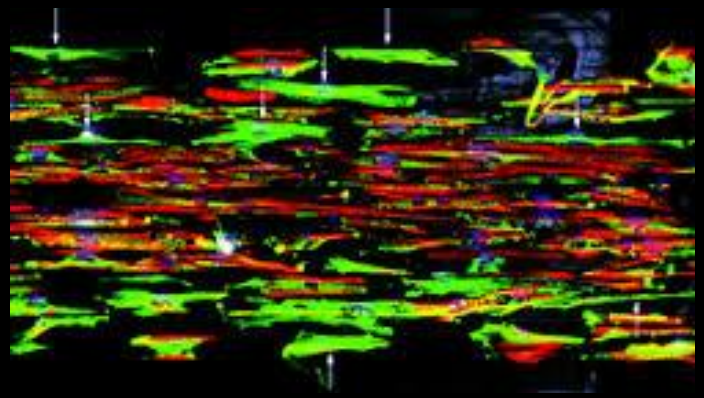




100s Diverse Neurons

Glia: Astrocytes &Oligodendrocytes





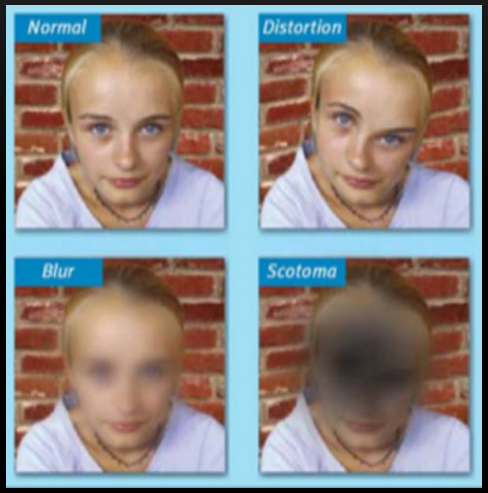
OUTLINE

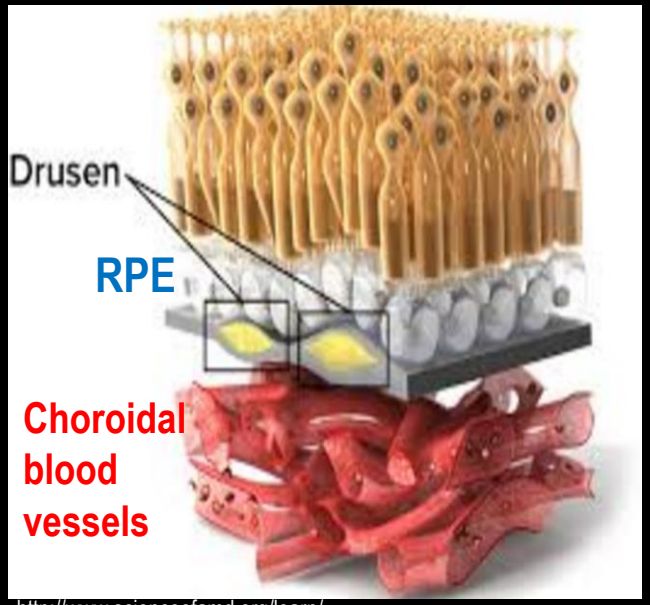
PROGRESS IN TRANSLATIONAL STUDIES

- Retinal Pigment Epithelium transplantation using Adult RPE stem cell
- Oligodendrocytes

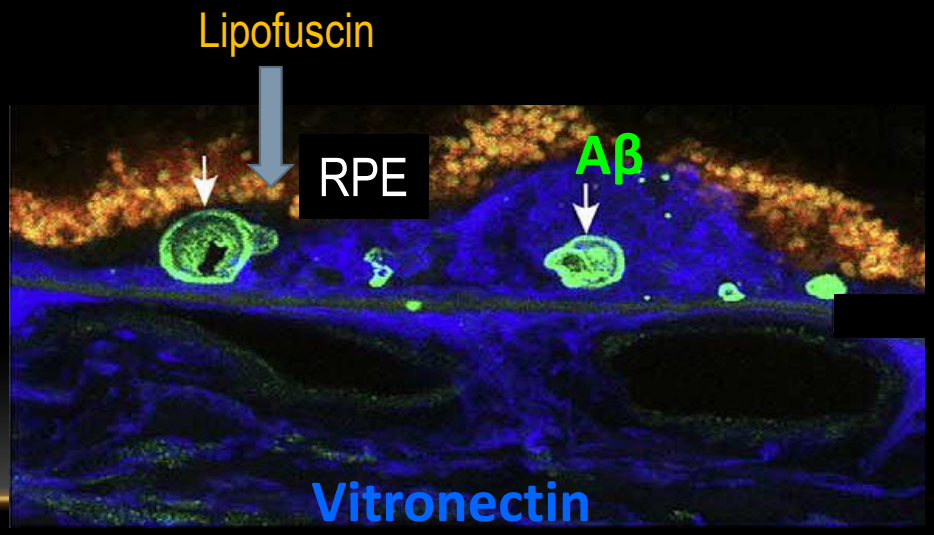
CHALLENGES/LESSONS LEARNED

REPLACING THE RPE IN AGE-RELATED MACULAR DEGENERATION

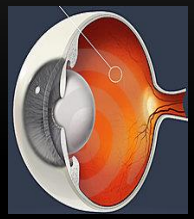


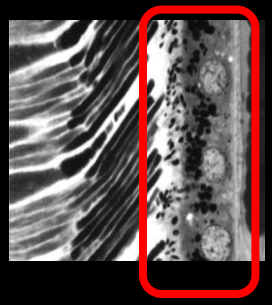


http://www.scienceofamd.org/learn/



ADULT RETINAL PIGMENT EPITHELIAL STEM CELLS (RPESCS): DORMANT STEM CELLS IN THE ADULT HUMAN RPE LAYER



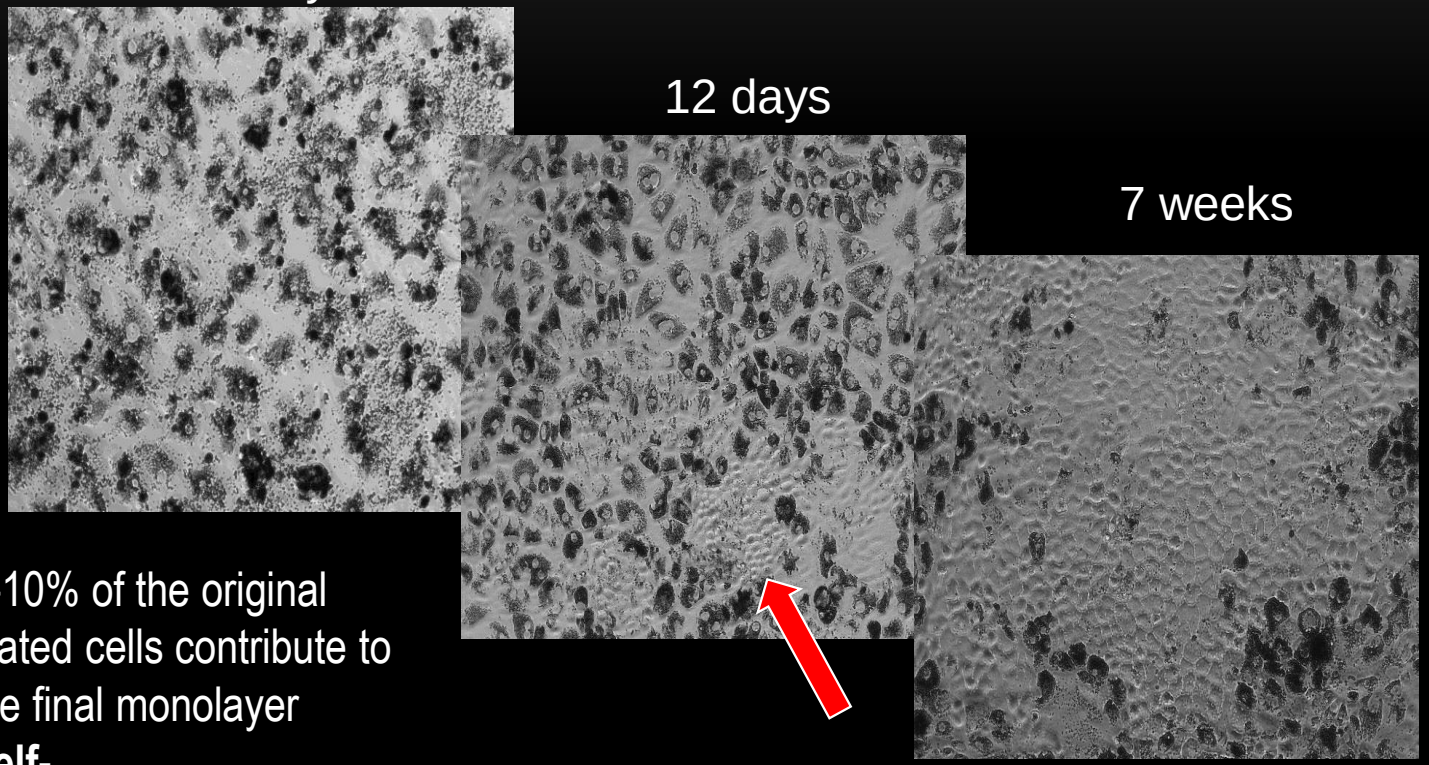


Normally dormant in adult

3 days

12 days

7 weeks



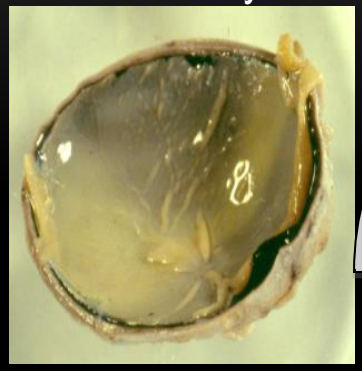
3-10% of the original plated cells contribute to the final monolayer **Self-renewing,multipotent**

Self-renewal
-time-lapse video
-sphere formation
-single cell clonal culture

The RPESC is Poised to make RPE

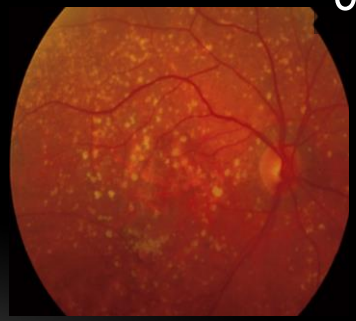
Transplantation of RPESC-RPE for AMD

Donated Eyes



Expand

Sub-retinal
Transplant
into disease area
50-150,000 cells

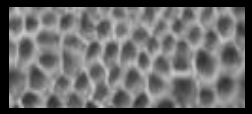


Translational Research Team

1. Cell manufacture Identity Purity Potency	2. Safety study GLP $$ millions	3. Animal efficacy -scientific rationale	IND FDA	Clinical Trial Phase I, II, III

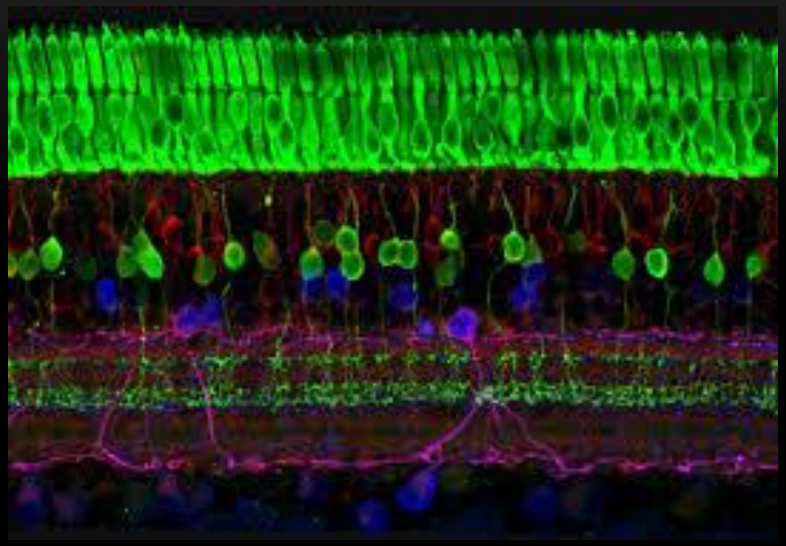
15-20 million dollars

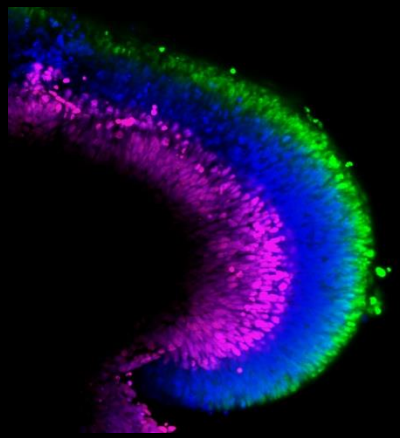
Sources of RPE for Transplant: Value of multiple studies if data is shared

Property \ Source	Embryonic stem cells	Induced pluripotent stem cells	Adult RPE stem cells 
Form tumors In Immuno-comp. mouse	Concern, but once highly differentiated, better	Concern, but once highly differentiated, better	No, to date **enables stages of maturation
Immuno-Suppression	yes	Allogeneic, Autologous possible	Allogeneic, Autologous possible
Expansion	unlimited	unlimited	5x10*8
Present in the adult eye	**No**	**No**	**Yes****

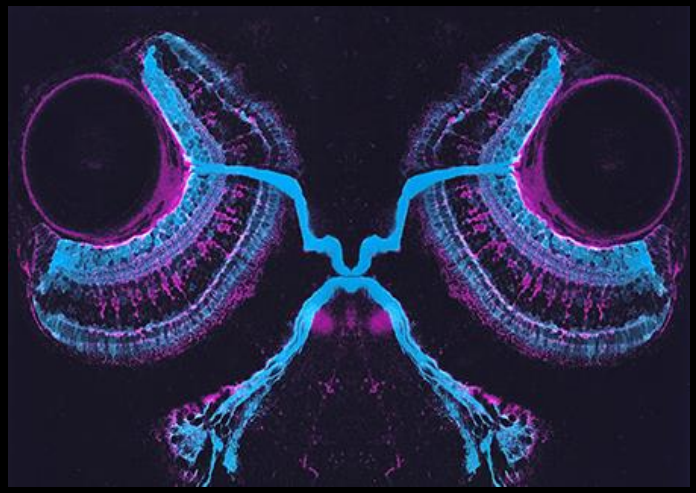
FUTURE RETINAL CELL REPLACEMENT

- Photoreceptor Replacement
  RPE+PR
- Additional retinal cell types
- Full thickness retina: 3D organoids



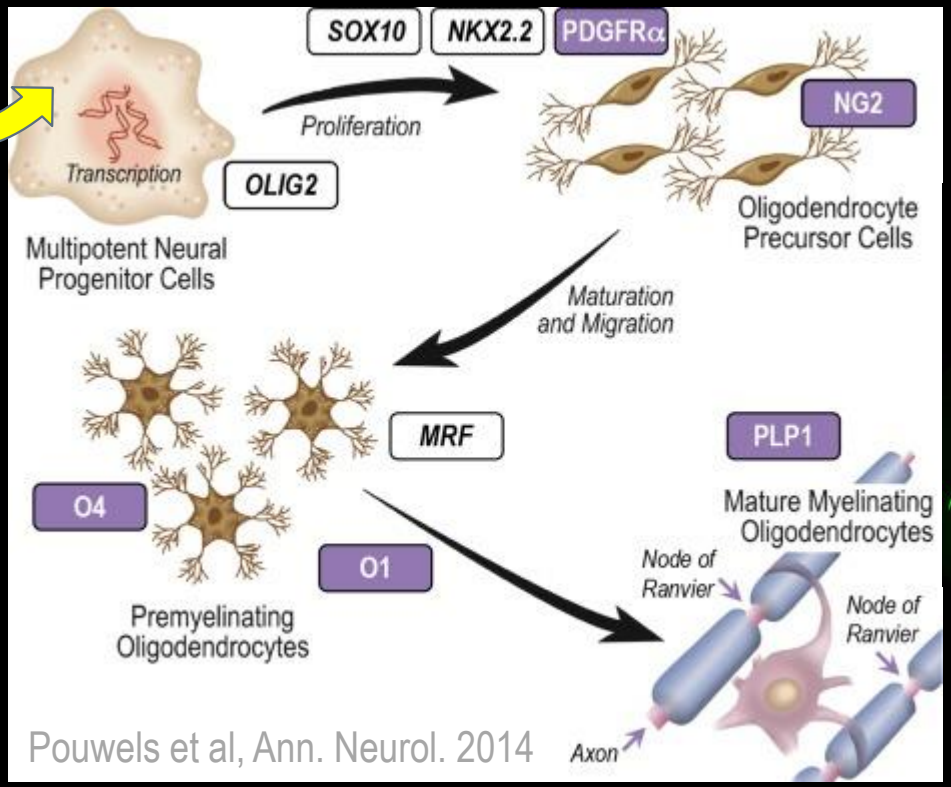


Retinal Ganglion Cell connectivity to the brain



PROGRESS: OLIGODENDROCYTE REPLACEMENT

Pluripotent stem cells



Pouwels et al, Ann. Neurol. 2014

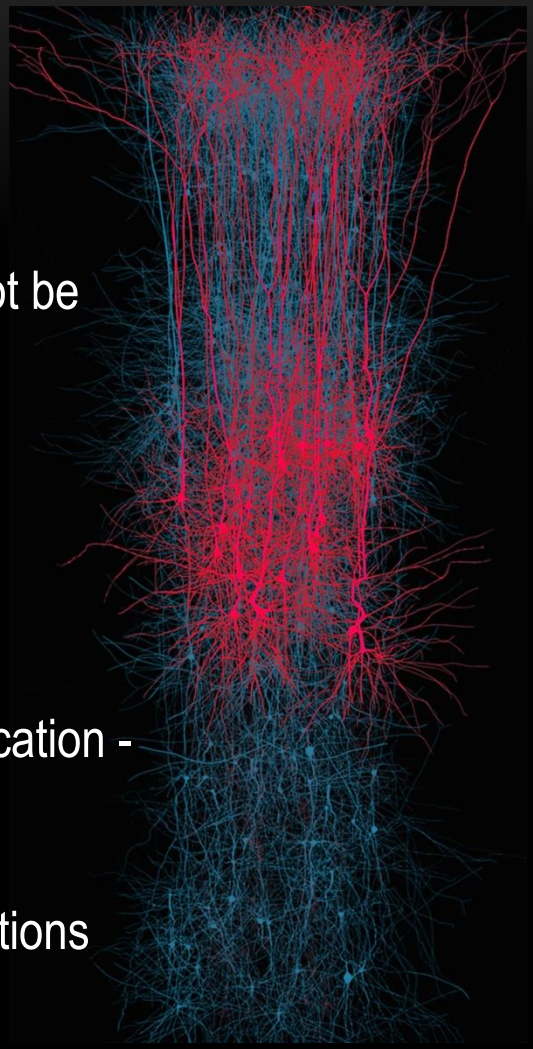
Leukodystrophies
e.g. Multiple Sclerosis
Spinal cord injury

Widespread migration and integration in mouse

Steve Goldman, Martha Windrem and colleagues

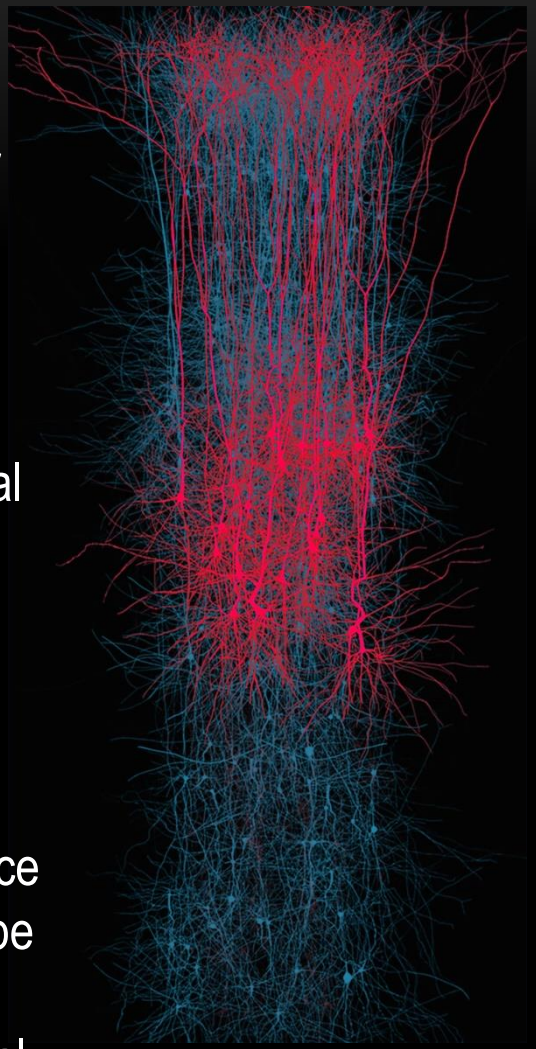
Optimal Stage

CHALLENGES/LESSONS LEARNED
1. CELL REPLACEMENT STRATEGY



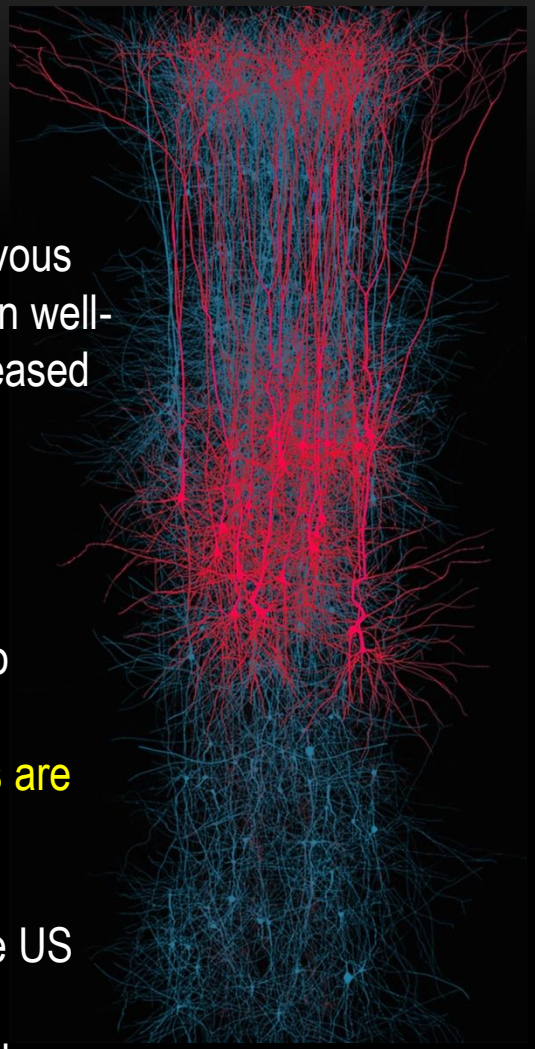
- Production of Authentic Cell Types from stem cells at sufficient identity/purity – how to define cells and heterogeneity?
- Identification of the optimal cell stage for transplantation, may not be mature cells
- Challenges in Delivery, Cell Integration, Survival
- Potency/ mechanism of action difficult to determine
- Functional recovery – evaluate for cell product and clinical application - long experiments, challenge in defining appropriate endpoints
- Immunosuppression – need to define for different neural applications
- Adverse events – monitor proliferation, differentiation, abnormal connections, disruption of neural function, pain

CHALLENGES/LESSONS LEARNED
2. TRANSLATION



- Appropriate animal models for efficacy are difficult to obtain for many diseases.
  - Can we augment with efficacy in the dish using 2D or 3D human stem cell models?
- Length and cost of safety studies
  - No evidence of adult stem cells causing tumors unless original cell was tumorigenic, substitute with sensitive in vitro tests
  - CRO, GLP, Millions of dollars, need to ensure studies are predictive and worth the time and cost
- Regulatory
  - Safety paramount
  - Benefit from more direct FDA input – differing consultant advice can be confusing; more ways to interact with the FDA would be beneficial
- Cost of overall of translation, 20MM preclinical, Cost clinical trial, multimillions
  - Need new models/opportunities to fund

CHALLENGES/LESSONS LEARNED
3. RISK TO PATIENTS & THE FIELD



- Advancing studies with poorly defined cell types
  Need expert input into cell generation
- Advancing studies with cells that are not normally present in the nervous system poses risk – lack of clear rationale and often not efficacious in well-controlled studies. Repeated injection of short-lived cells poses increased risk: e.g. Umbilical cord cells, Mesenchymal 'stem' cells
- Lack of data sharing/tension with confidentiality
  Proprietary cells
  Proprietary processes
  Sharing information on failures as well as successes is beneficial to advance new efforts
  Accurate reporting – including to the press – is required so patients are properly informed
- Unproven therapies
  Safety is paramount, but clinics are springing up in their 100s in the US and worldwide, need better policing to protect the public
  More public education is needed to advise patients, advocates and clinicians, eg ISSCR Website Closer Look at Stem Cells
  http://www.closerlookatstemcells.org/

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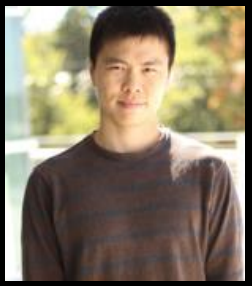

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