

MEDICAL MANAGEMENT OF THYROID EYE DISEASE

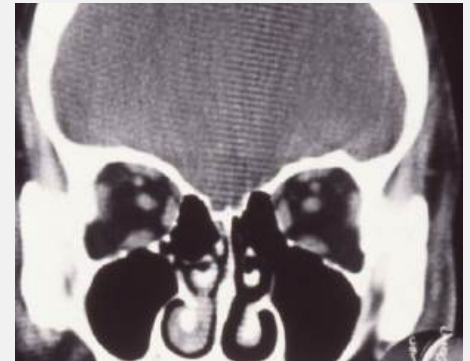


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LECTURE GOALS

- Profile **at Risk** TED patient
- Thyroid stimulating immunoglobulin helps predict who will respond to medical therapy
- Smoking makes medical RX less effective
- Review medical therapeutics



NATURAL HISTORY CURVE OF TED ACTIVITY



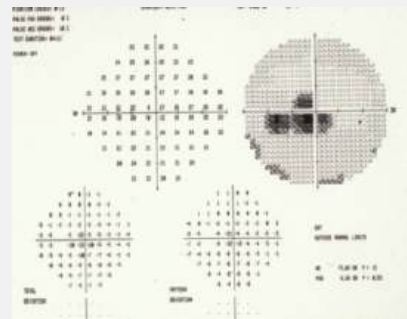
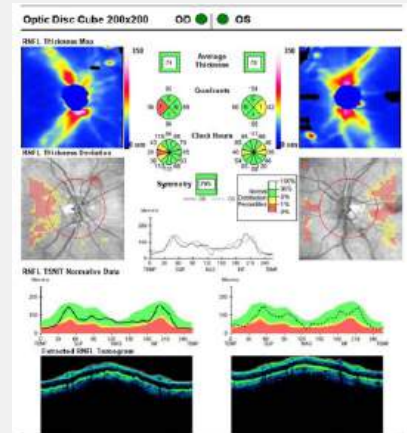
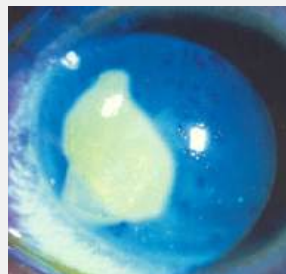
- **Worsen – Stabilize - Improve**
- Inflammation and Congestion
- Proptosis and Eyelid Retraction
- **Dysmotility**

**WE CURRENTLY RELY ON
KNOWN RISK FACTORS TO
PREDICT DISEASE
SEVERITY**



KNOWN RISK FACTORS FOR SEVERE ACTIVE TED

- ✦ Tobacco
- ✦ Male gender
- ✦ Age > 50 years old
- ✦ Untreated hypothyroidism
- ✦ Radioactive Iodine (RAI)

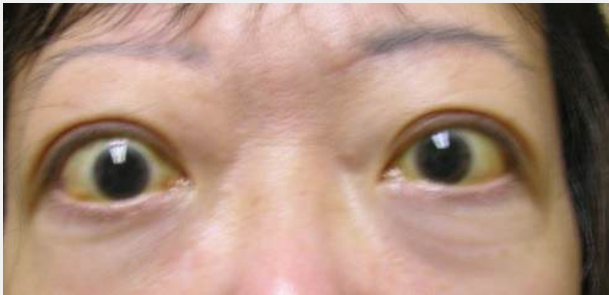


CIGARETTE SMOKING STRONGEST MODIFIABLE RISK FACTOR

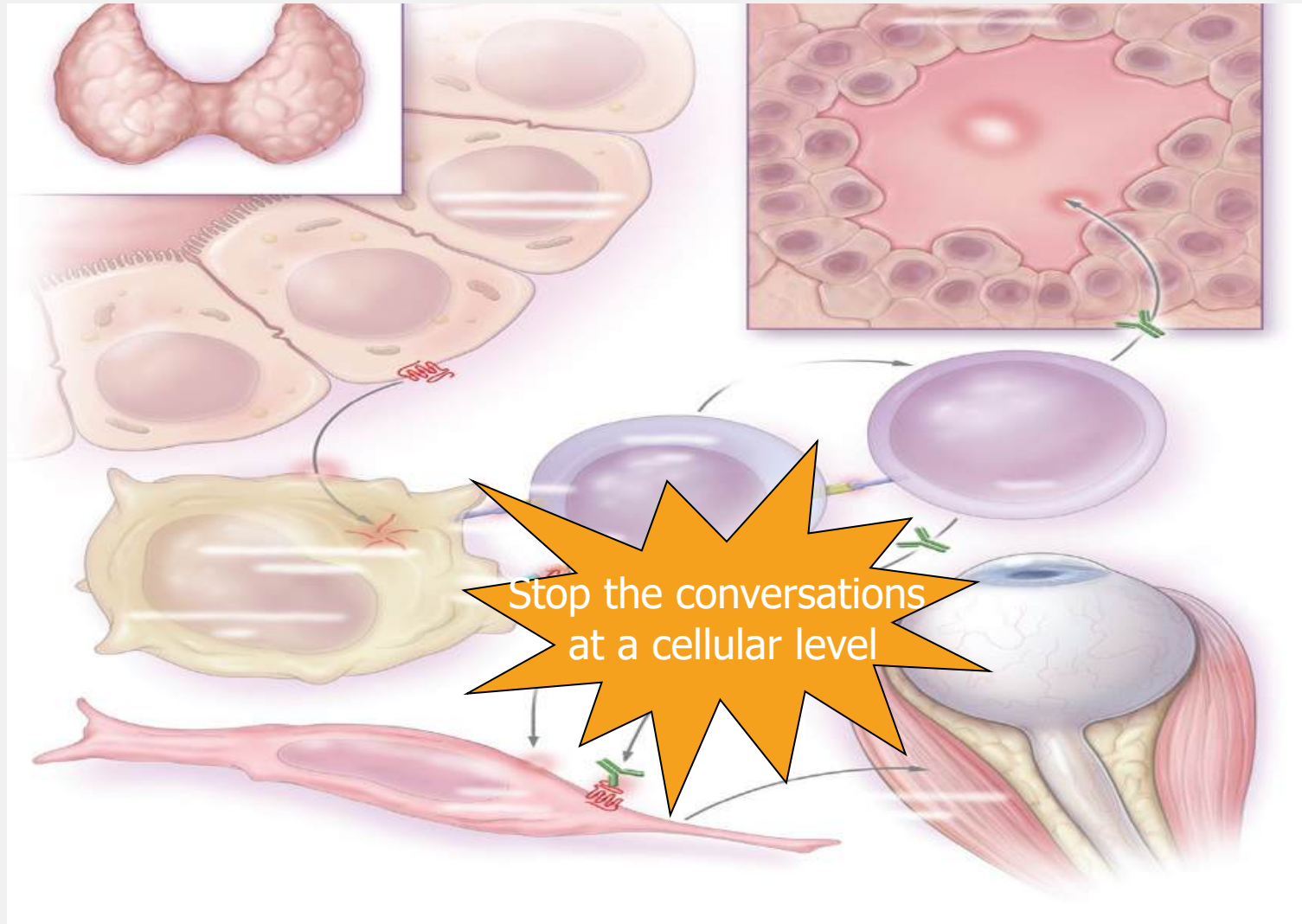
- Proportional # per day
- Severe TED more likely
- Signs more prolonged
- **Less responsive to medical therapies will likely need surgery**



NO CONSENSUS: MEDICAL THERAPY
EFFICACY
MUSCLE VS. FAT ----ETHNICITY DIFFERENCES



Goal of Medical Therapy = stop Cellular Conversations



TSI

- Significantly higher GD pts with TED
- **Correlates well with active TED signs**
- Higher when EOM and fat expansion are both present on orbital imaging

MEDICAL OPTIONS

- Corticosteroids
- 5FU
- Restylane
- Radiation
- Immunomodulation
 - -Retuximab

CORTICOSTEROIDS

- Oral Prednisone
- Pulse IV methylprednisolone
- Peribulbar steroids
- Topical steroids
- **Intranasal steroids**

Corticosteroid Regimens

Oral: 20 mg q am increase 10 mg per week until symptoms improved – keep at that dose for one month – then taper 1 mg per until week

IV: 250 mg methylprednisolone weekly for six weeks (combine with nasonex if possible)

Intra-orbital: make an incision superomedial and use an 18 guage angiocath to drip 50:50 mix of kenalog 40 and 5FU 35 mg/ml

ORAL AND IV CORTICOSTEROIDS DEplete BONE

- Increase osteoclast activity
- Increase urinary calcium loss
- Inhibit intestinal uptake of Vit D
- Secondary hyperparathyroidism
- Suppress bone growth
- All of these changes work together to deplete bone

Superomedial orbitotomy – remove
intraconal fat – use angiocath to drip
In the corticosteroid and 5FU



Contraindicated in
Steroid responder

NASONEX: EFFICACY INTRANASAL DELIVERY TO ORBIT

- **No ocular irritation**
- **Highest Potency**
 - Most effective at inhibition of T cell cytokine production
 - Highest glucocorticoid receptor binding affinity
- **Highest Lipophilicity**
 - Increased and faster uptake by mucosa
 - Greater retention in absorbing tissue

NASONEX: SAFETY PROFILE

- No hypothalamic-pituitary-adrenal axis suppression
- No growth retardation in children
- No bone loss in Adults

NASONEX: RESULTS

- 28 women; four men
- TSI 285 - 819
- All had improved clinical activity score and TEDQOL when treated with Nasonex BID
- Effects first noted 3 -7 days after initiation of treatment. Average duration of use 6 months.

NASONEX: SIDE EFFECTS

- **Blood in nasal mucous but no epistaxis** – can be prevented by having patient direct the spray toward the orbit –not the septum
- **Sore Throat** – can be prevented by having pts gargle after use with water

EFFICACY OF XRT (BARTALENA, 2003)

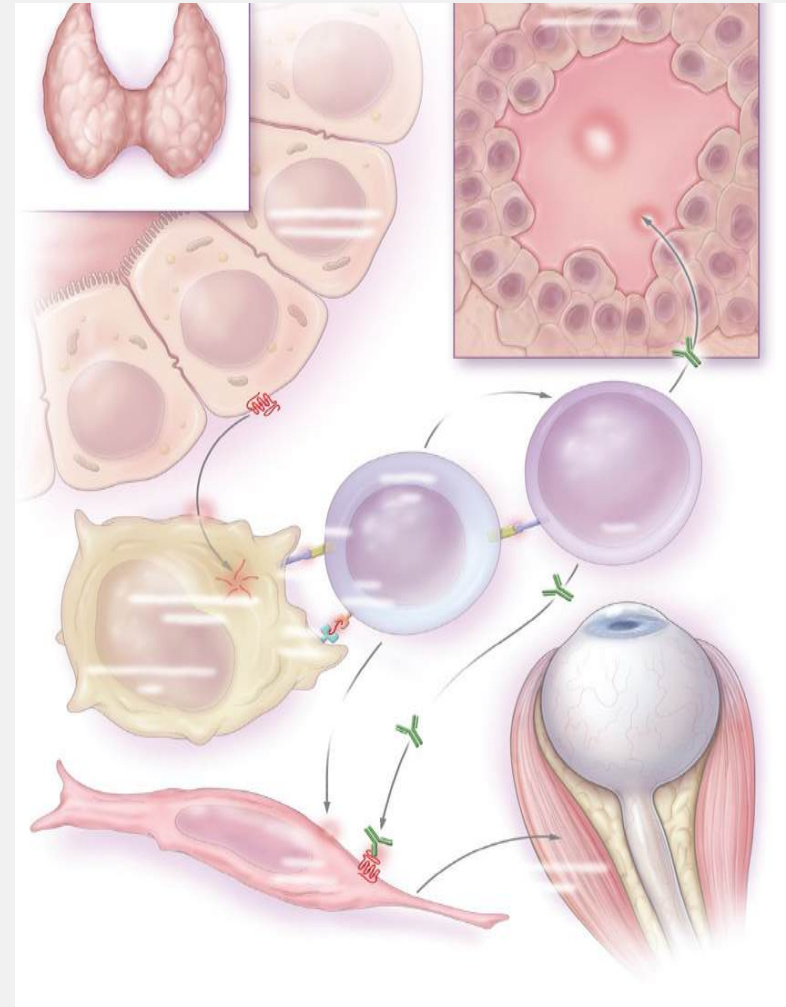
- 1973 – 2001
- 25 studies
- 1,014 patients
- Favorable response: 0* – 96 %
- Mean: 57%



* Gorman 2001

RETUXAMAB AND OTHER IMMUNOMODULATORS

- Reserved for treatment failures
- Requires hospitalization
- Morbidity and mortality possible



THE FUTURE: LOCALLY DELIVERED THERAPEUTICS

- Small molecules
 - Corticosteroids
 - Immunosuppressives – 5-FU
- Large molecules
 - Anti-T cell
 - Anti- B cell
 - Other ?

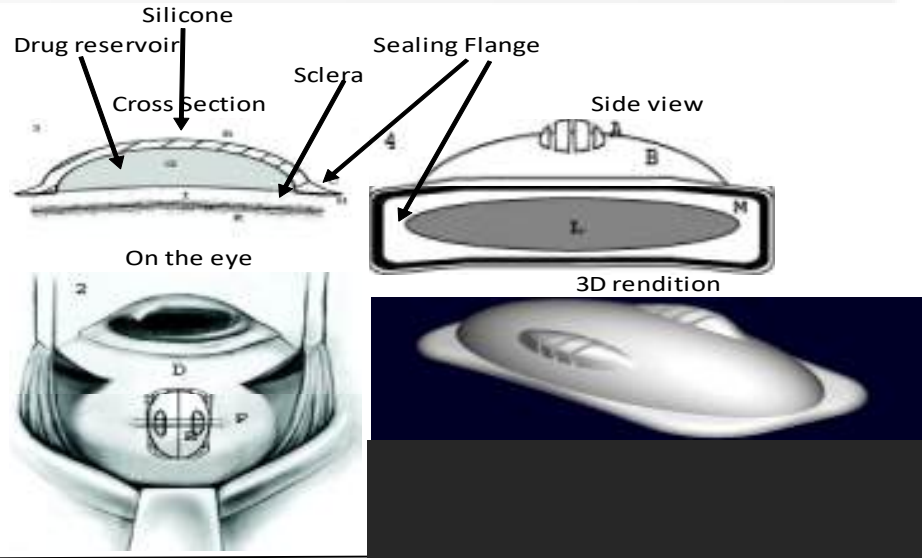
Episcleral Therapy for IED Related Ophthalmic Injury

PI: Ricardo Carvalho, MD/PhD

Org: Targeted Therapy Technologies, LLC

Problem, Hypothesis and Military Relevance

- **Unmet medical need:** Blinding TBI/traumatic ophthalmic injuries.
- **Rationale:** With a unique ophthalmic episcleral device that can be placed in theater, we will test the ability of two drugs (with already proven retinoprotective efficacy) to prevent visual loss and forestall blindness in animal models of TBI/traumatic injury.
- **Relevance:** Such injuries are pressing concerns in Iraq and Afghanistan. The Blinded Veterans Association reports that 64% of those with TBI test positive for visual dysfunction.
- **Experimental design** will include necessary animal studies to prove efficacy and safety of this intervention and studies necessary for filing of Investigation New Drug applications with the FDA and military research committees.



Proposed R&D Goals

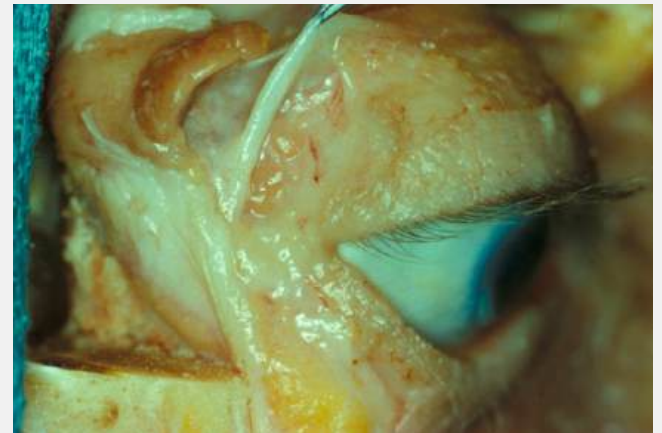
- **Translation to practical application:** Characterize critical parameters for dose/formulation based on demonstrated efficacy and safety;
- **Regulatory goals:** Meet regulatory requirements for clinical testing of two drugs used to prevent or minimize visual loss due to TBI.
- **Ultimate goal:** Both drugs will be delivered to the posterior segment at concentrations necessary to prevent RGC/photo receptor loss in animal models of traumatic optic neuropathy. Following, IND enabling GLP ocular safety and PK studies will be complete along with clinical supply manufacture.
- **Proposal for clinical development:** A clinical advisory committee with expertise in medical care of military personnel, will oversee and propose the clinical development pathway to be followed.

Timelines

Activities	2010	2011	2012	2013
Formulation/sample preparation, in vitro, ex vivo, in vivo ocular pk and prelim. tox	■			
IND Enabling studies: GLP Ocular safety and PK		■		
Mfr of clinical supplies and CMC work; clinical advisory committee clinical development/application strategy			■	

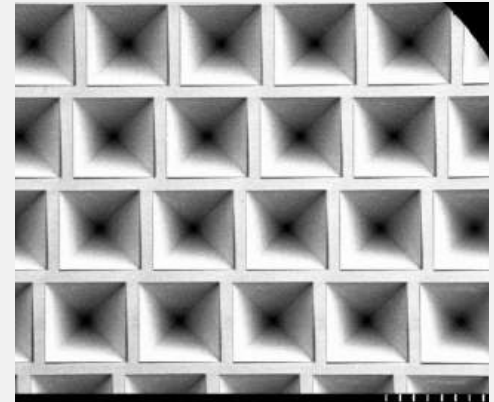
MEDICAL APPLICATION OF MEMS...

- **Nanoparticles**
 - Increase bioavailability
 - Decrease systemic toxicity
- **Implantable devices**
 - Sense biologic need
 - Respond with drug delivery

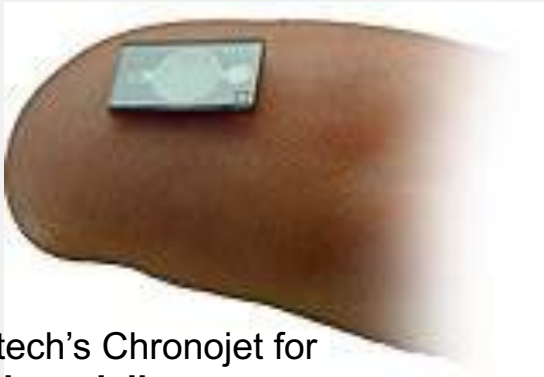


CHANNELS CAN SUCK OR SQUIRT

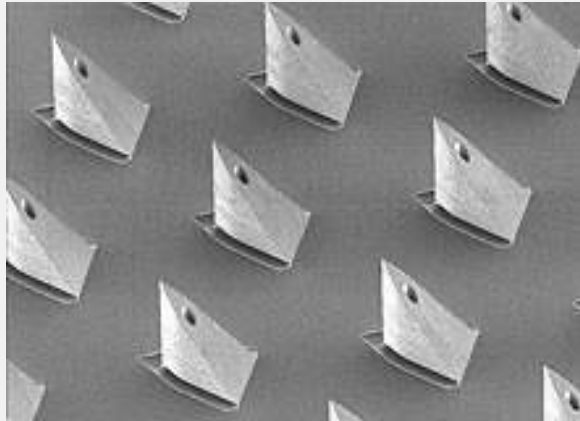
- External electrical current →
- Incorporated gold or platinum adjacent to micropores →
- Fluid flows through the channels
 - Outward (drug delivery)
 - Inward (substrate detection)



EXAMPLES: MEDICAL MEMS



Debiotech's Chronojet for **drug delivery**

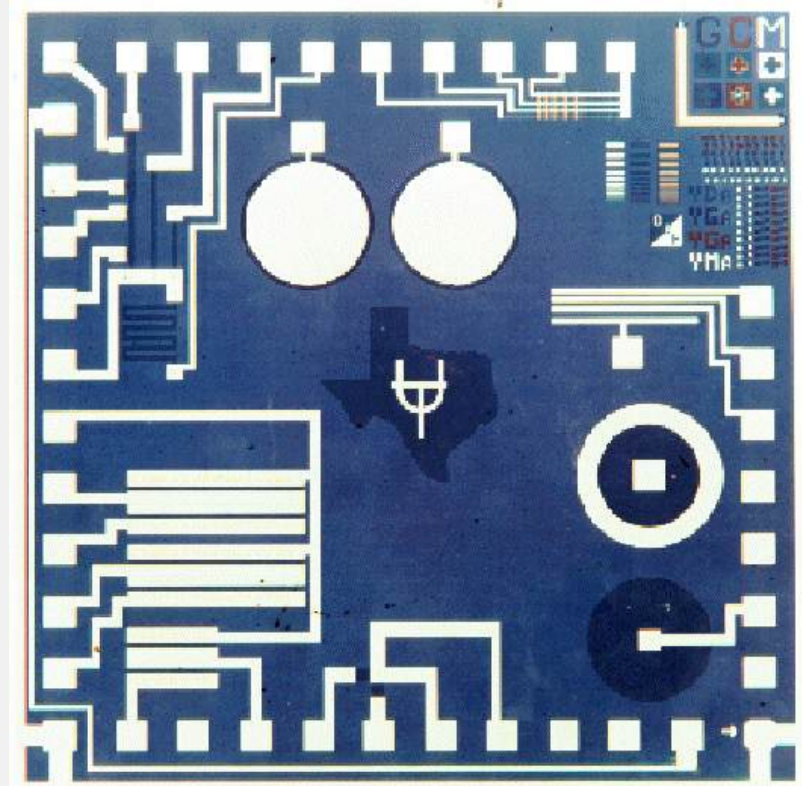
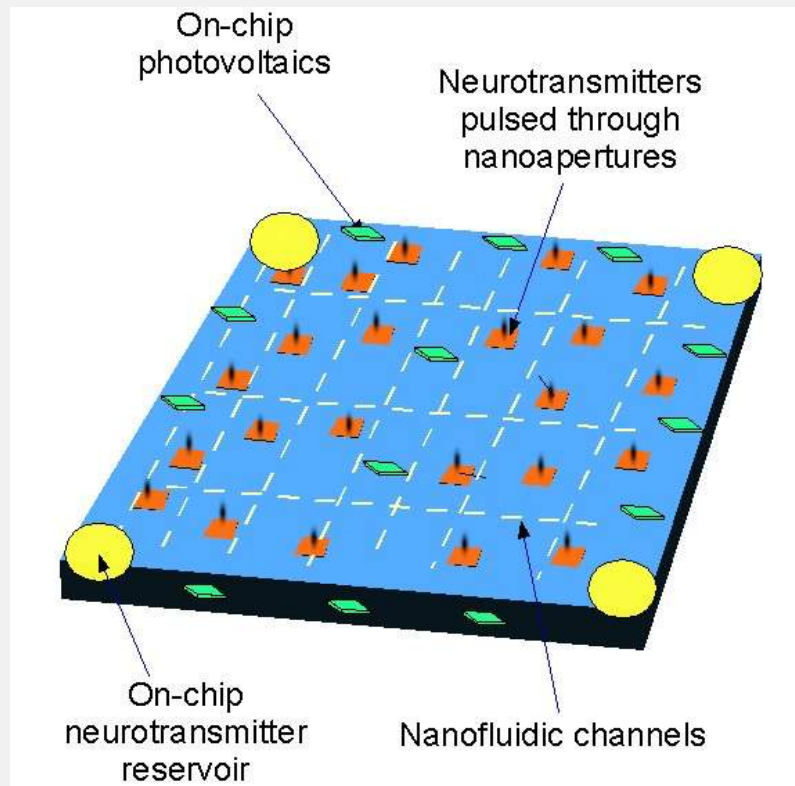


Silicon **microneedles**: Silex Microsystems, Sweden



Prototype assembly of an **implantable retina**: D. Baldwin, et. al, Engent; D. Shire, VA/Boston Retinal Implant Center

HYBRID ELECTROCHEMICAL CHIP THE FUTURE ?



SUMMARY

- **There is an unmet clinical need**
 - **Inflammation -> Fibrosis**
 - **Systemic therapeutics -> toxicity**
- Current local therapeutics not ideal
- We should translate existing technology to create local delivery systems
- Small molecule delivery the easiest
- Ideally would deliver monoclonal antibodies

THANK YOU!

