# Different Anti-Vascular Endothelial Growth Factors

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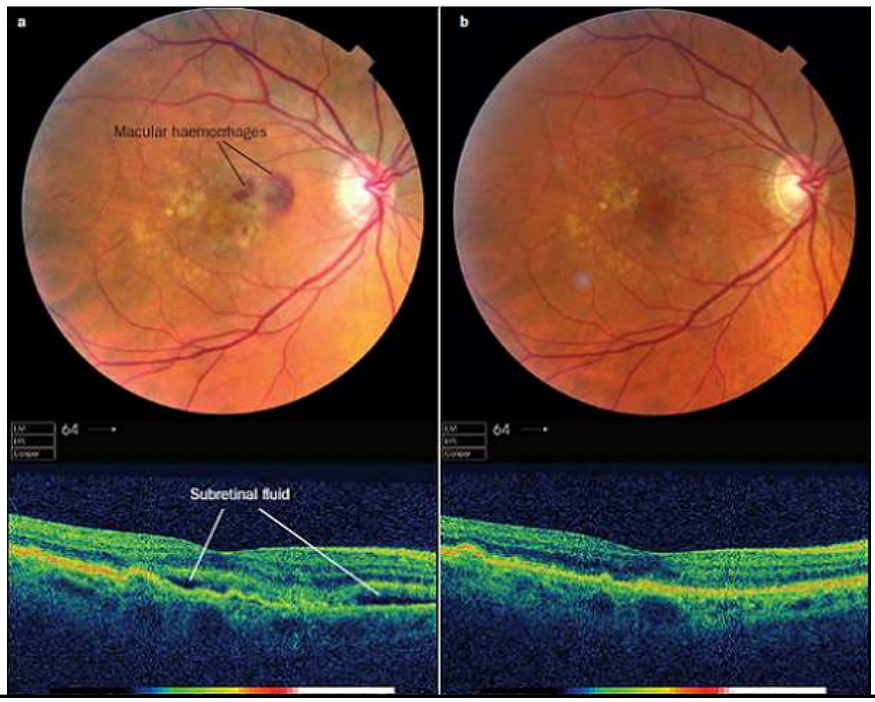
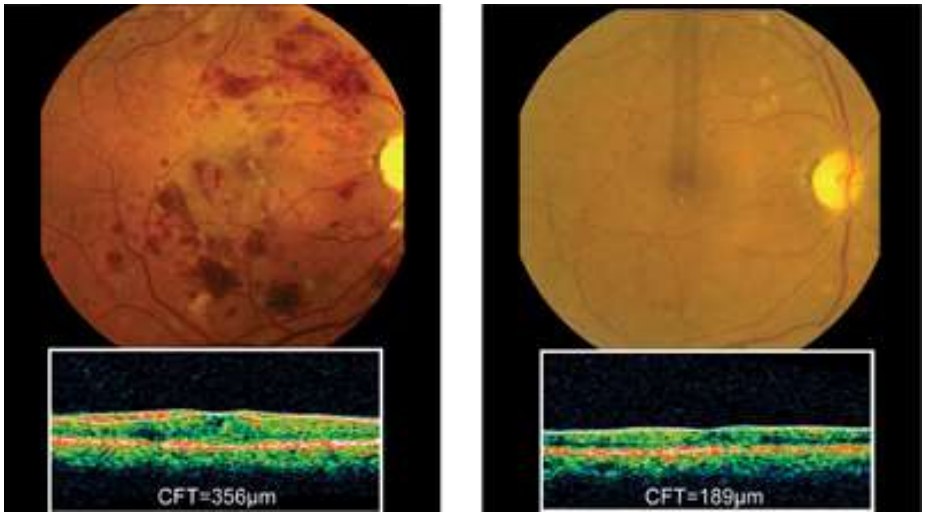
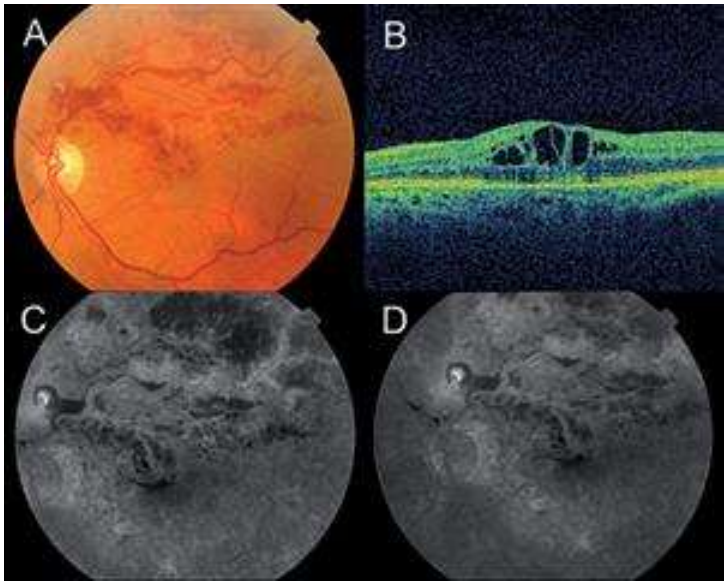
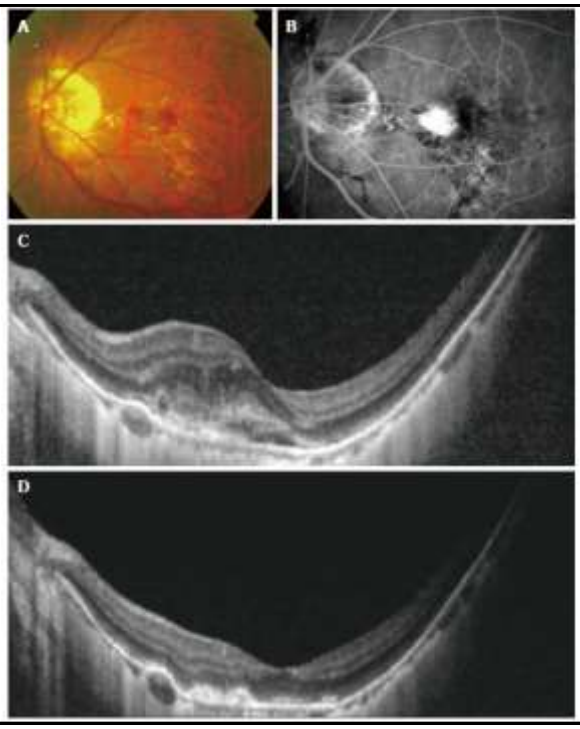



CFT=356µm
CFT=189µm


A
B
C
D

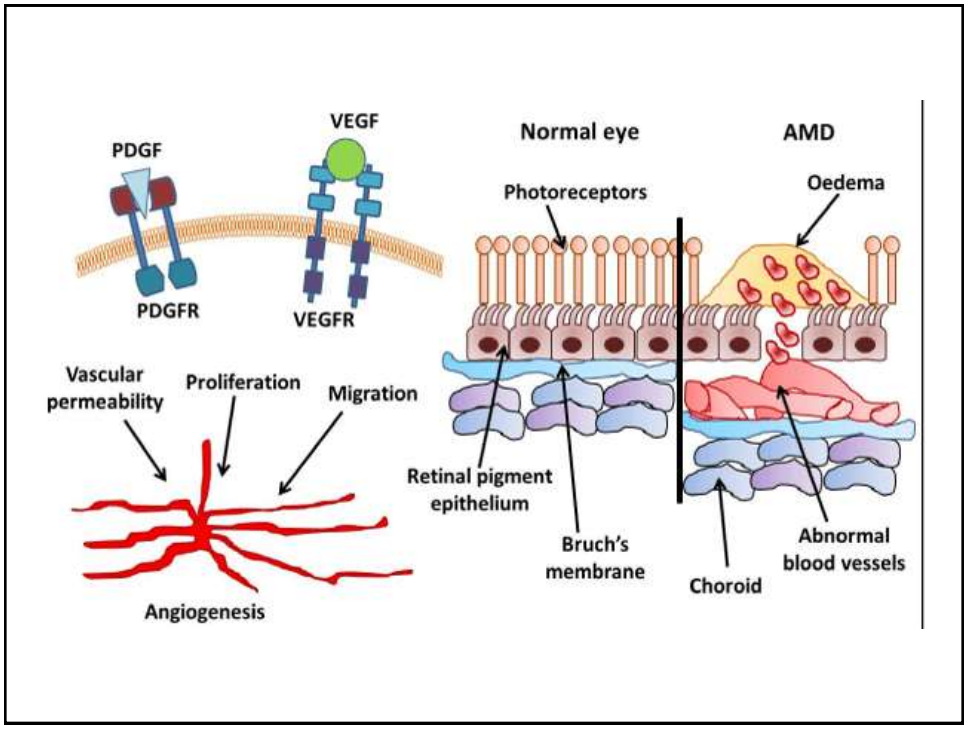


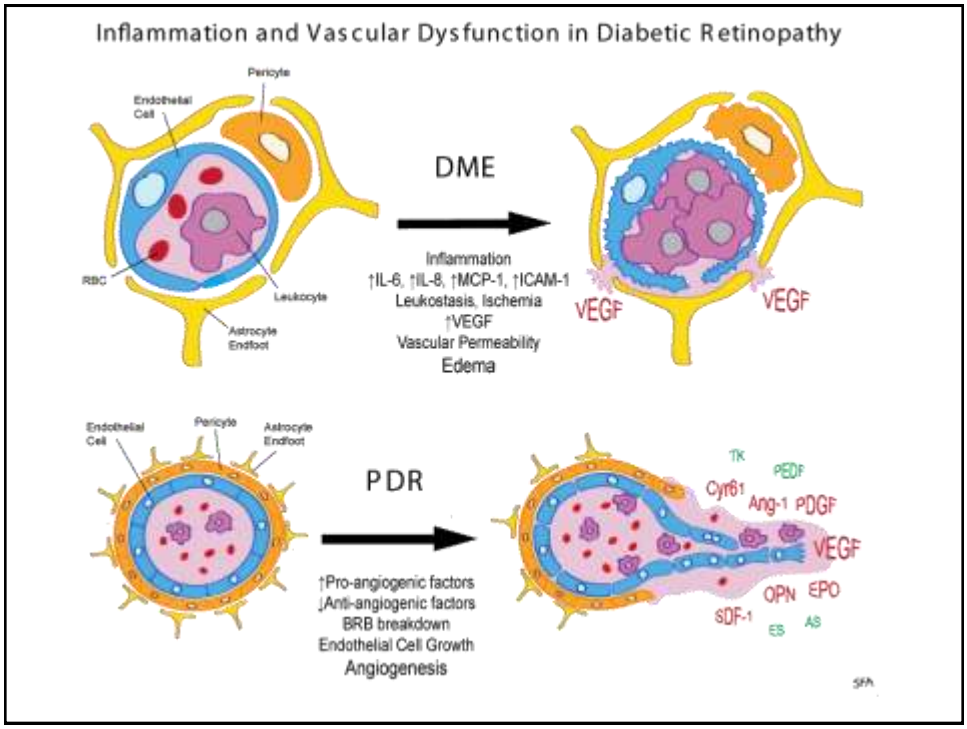

- Before the development of anti-VEGF therapies, these conditions were most often treated with a combination of ablative and non specific laser treatment or were simply given careful observation and monitoring , with a universal decline in vision.

- The current use of anti-VEGF treatment has resulted in improvement of visual outcome and has changed the standard of care in retinal medicine and ophthalmology.

- In 1989: ferrara & his colleagues at Genentech were the first to isolate and clone VEGF
- In 1993: ferrara reported that inhibition of VEGF-Induced angiogenesis by specific monoclonal antibodies resulted in dramatic suppression of the growth of a variety of tumors in vivo.
- In 1994: American journal of pathology published: hypoxic retina produce VEGF
- In 1996: studies showed evidence of a direct role for VEGF to induce new vessel growth and increase permeability

- VEGF has a role in normal vascular growth (normal angiognesis)
- But VEGF is responsible for many retinal diseases by causing new vessel growth (abnormal angiognesis ) and increase leakage.


PDGF
VEGF
PDGFR
VEGFR
Vascular permeability
Proliferation
Migration
Angiogenesis
Normal eye
AMD
Photoreceptors
Oedema
Retinal pigment epithelium
Bruch's membrane
Choroid
Abnormal blood vessels


Inflammation and Vascular Dysfunction in Diabetic Retinopathy
Pericyte
Endothelial Cell
RBC
Leukocyte
Astrocyte Endfoot
DME
Inflammation
↑IL-6, ↑IL-8, ↑MCP-1, ↑ICAM-1
Leukostasis, Ischemia
↑VEGF
Vascular Permeability
Edema
VEGF
VEGF
PDR
↑Pro-angiogenic factors
↓Anti-angiogenic factors
BRB breakdown
Endothelial Cell Growth
Angiogenesis
TK
PEDF
Cyr61
Ang-1
PDGF
VEGF
OPN
EPO
SDF-1
ES
AS

- VEGF is a gene.
- There are 7 different families:
  - VEGF A
  - VEGF B
  - VEGF C
  - VEGF D
  - VEGF E
  - VEGF F
  - PLGF – placental growth factor
- VEGF A → 6 isoforms

  These isoforms have 121,145,165,183,189 and 206 aminoacids.
- VEGF 165 exists in both soluble and bound forms and is thought to be predominantly responsible for pathologic neovascularization.

VEGF exerts its effect on cells through two highly related receptor tyrosine kinases VEGFR-1 and VEGF R-2

- VEGFR-1 is a decoy receptor which downregulates the activity of VEGF
- VEGFR-2 bind to VEGF with lower affinity relative to VEGFR-1

So, VEGF neutralizing strategy work through VEGF inhibition by one of the following:

- Direct inhibition of the isoforms by use of monoclonal Abs.
- Receptor blockage through
  - Native decoys
  - Tyrosine kinase inhibitors
  - Fusion proteins
- Interruption in the downstream intracellular signaling pathogenesis.

## VEGF-Neutralizing Strategy

- The first treatment developed using a VEGF-neutralizing strategy was Bevacizumab (Avastin, Genetech Inc.).
- Bevacizumab is a humanized full length anti-VEGF antibody designed to block all VEGF isoforms.
- In 1997:Genetech inhiated phase 1 trials of bevacizumab for treatment of cancer then completed phase 2 & 3.
- In 2004: 0n February 26 Bevacizumab was approved by FDA for treatment of colon cancer in combination with chemotherapy.

- Concomitant with the development of anti-VEGF therapies for cancer , VEGF was found to play a pivotal role in neovascular AMD
- One of the first anti-VEGF therapies for NVAMD was Pegaptanib (Macugen)
- Pegaptanib (Macugen, Eyetech pharmaceuticals & Pfizer, NY) is an RNA aptamer that binds and neutralizes VEGF 165.

- After RCTs, Pegaptanib was approved by the FDA in 2004, December 17 for the treatment of NVAMD.
- It showed improvement in visual & anatomical outcome but it was minimal probably because it binds to a single isoform.
- After approval of Bevacizumab for cancer therapy and given the suspected role of VEGF in NVAMD, systemic intravenous Bevacizumab began to be administered to treat NVAMD as an off-label use and showed significant improvement in VA & retinal thickness on OCT.

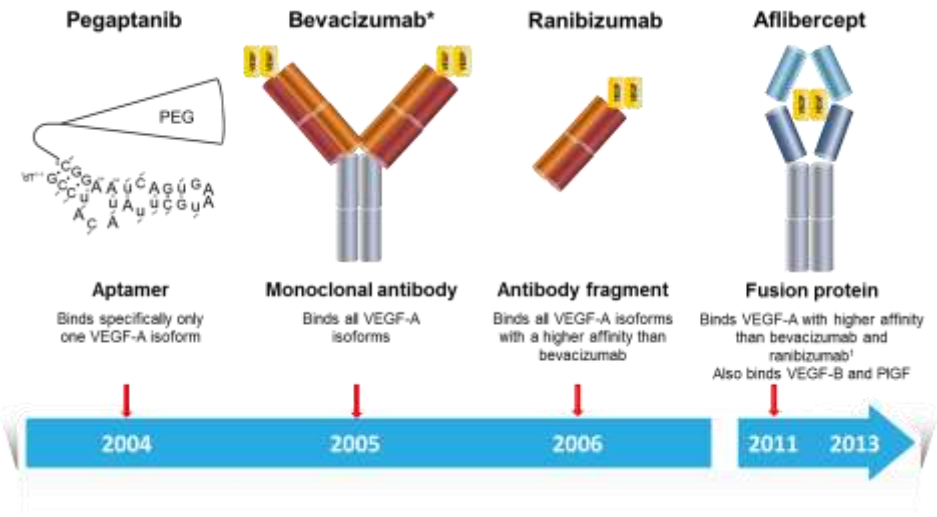
- At that time, Intravitreal Bevacizumab was not regarded a useful agent for the treatment of AMD because this full-length antibody was not believed to be able to penetrate the retina, according to the observation that molecules larger than 77 kDa could not freely diffuse across human retina.
- However in 2005 Rosenfeld et al. reported that VA & macular appearance on OCT were improved after single eye treatment of NVAMD with intravitreal Bevacizumab.

- Soon after, Ophthalmologists began injecting Bevacizumab directly in the vitreous Cavity as an off-label use in the treatment of NVAMD.
- It was found to be effective with minimal systemic adverse effects.

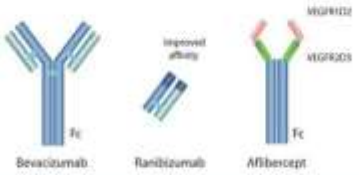
- Ranibizumab ( Lucentis, Geneteh pharmaceuticals) is humanized anti-VEGF recombinant Fab fragment ( 49 kDa)
- It binds with VEGFR-binding domain of all biologically active isoforms of VEGF-A.
- In 2006: Ranibizumab was approved by FDA for treatment of NVAMD.

- Aflibercept (VEGF-Trap) ( Eylea Regeneron pharmaceuticals)
  - It is a high affinity antagonist of VEGF consisting of the immunoglobulin domain 2 of human VEGFR-1 and domain 3 of human VEGFR-2 fused to Fc fragment of human IgG (fusion proteins )
  - It has unique binding mechanism ( two hands on a ball)
- Aflibercept exhibits a binding affinity near 0.5 Pmol/L compared with 50 Pmol/L for Ranibizumab or Bevacizumab which represents a 100-fold increase in binding affinity.

- The intravitreal half-life of Aflibercept is 4.8 days compared with 3.2 days and 5.6 days for Ranibizumab and Bevacizumab respectively.
- In 2011: Aflibercept was approved by FDA for treatment of NVAMD.



# Differences in Anti-VEGF agents




| | Ranibizumab | Bevacizumab | Aflibercept |
|---|---|---|---|
| Molecule | Fab | Full –sized Mab | Fusion protein |
| Binds | VEGF -A | VEGF-A | VEGA-A, B and PIGF |
| Fc | No | Yes | Yes |
| Mol wt | 48kDa | 149kDa | 115kDa |
| Intravitreal VEGF binding activity (Mathematical model) | 30 days | 27-38 days | 83 days |

# Which anti-VEGF & How frequently to inject?

Although there is strong evidence that the use of anti-VEGF improve VA & dry the macula. However,

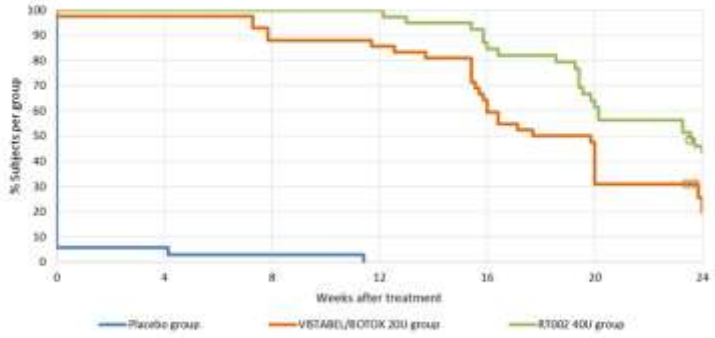
- Many patients respond poorly to anti-VEGF
- The resolution of fluid is transient
- The resolution is not complete

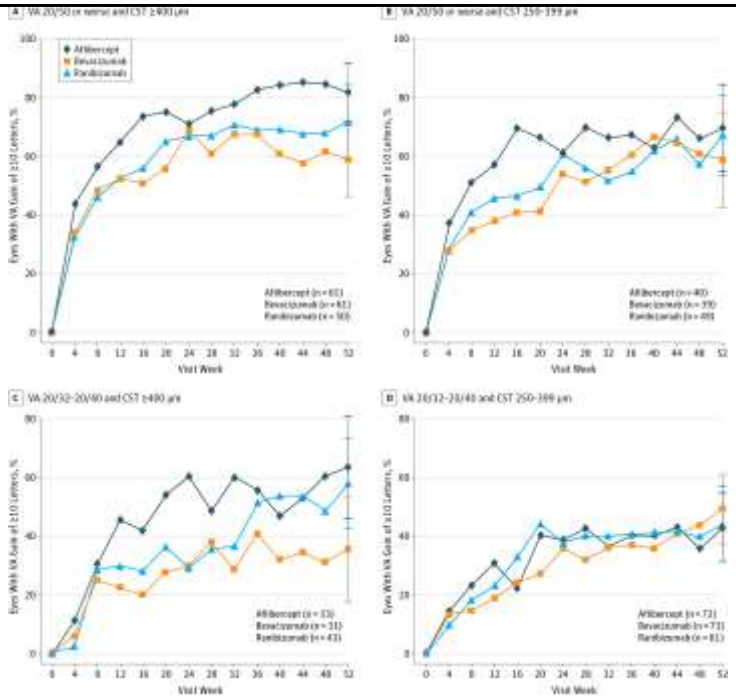
For example: In DRCR.net protocol I study, 50% of patients had persistent macular thickening even after one year of monthly injections.

- For AMD, after many studies like CATT study, VA gains were not maintained.
- This means the response to anti- VEGF is variable.


## Duration of Effect Separates RT002 from BOTOX

Kaplan-Meier Curve: Duration of Response for at least a 1-point improvement from Baseline for IGA-FWS Assessment (Per-Protocol Population)





## Four-dosing strategies:

1. Fixed monthly or bimonthly.
2. PRN (pro re nata).
3. Treat and extend.
4. Observe and plan.

1. Fixed stratgy:
   - Anti-VEGF agents given at a fixed monthly interval.
   - Once disease stability is achieved the follow up and treatment plan are tailored according to clinical status and judgment of the treating physian, in an attempt to reduce the treatment frequency and inconvenience on patient's life.

2.PRN strategy:
   - The retreatment is an individualized regimen based on monthly evaluation visits to detect early disease recurrence.
   - This regimen allows for reduced number of injections, however the tremendous burden of monthly visits on patients and health care systems is unresolved.

## 3. The treat and extend regimen:

- It is based on progressive lengthening of the intervals between the visit-injection dates.

  Each visit is combined with an injection and the visit result determines the subsequent interval to the next visit-injection date.

- It allowed for reducing the number of injections and simultaneously the number of visits with lower costs compared with fixed monthly retreatment along with maintaining an overall good VA outcome.

## 4.The observe and plan:

It is based on an initial three loading doses, followed by a monthly observation , once signs of recurrence appeared an OCT , the ideal treatment interval is considered to be 2 weeks shorter than the elapsed interval. Subsequently this interval is then applied for several fixed injections with intermittent evaluation. Monitoring visits following each series of injections aim to tune the interval in the subsequent injection series.

## Cost effectiveness

- Cost effectiveness of Aflibercept, Bevacizumab and Ranibizumab for DME treatment analysis from the DRCR.net comparative effective trial.
- In this randomized trial comparing anti-VEGF agents for patients with decreased vision from DME found that at 1 year Aflibercept (2.0 mg) achieved better visual outcomes than repacked (compounded) Bevacizumab (0.3 mg) or Ranibizumab (0.3 mg); the worse the starting vision, the greater the treatment benefit with Aflibercept. However, Aflibercept and Ranibizumab respectively are approximately 31 and 20 times more expensive than Bevacizumab .

Incremental cost- effectiveness ratios (ICERs)

- It is statistic used in coat-effectiveness analysis to summarize the cost effectiveness of a health care intervention.
  It is defined by the difference in cost between two possible interventions divided by the difference in their effect.

Quality adjusted life years (QALYs) is a generic measure of disease burden including both the quality and the quantity of life lived. It is used in economic evaluation to asses the value for money of medical interventions.

One QALY equals one year in perfect health.

## Future strategies Anti-VEGF therapy

1. Higher dose of anti-VEGF.
2. Long-lasting anti-VEGF delivery.

## Newer Anti-VEGF agents

1. Small interfering RNAs ( SiRNAs bevasiranib Opku Health)
2. Rapamycin (sirolimus, Macusight)

# Thank You