Five Trends in Ophthalmic Innovation Poised to Impact Global Eye Health

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Clarus Ventures, LLC
Financial Disclosures

“What Conflict of Interest?  
I work here in my spare time...”
Savage Chickens

by Doug Savage

IN THIS INFINITELY COMPLEX WORLD, HOW CAN I HELP BUT BE PLAGUED BY SELF-DOUBT?

I'M THE GREATEST!!

Prognosticators ...

© 2009 by DOUG SAVAGE

www.savagechickens.com
1 - Funding
Largely / Increasingly Private
(Private Equity / Corporate)
NEI Funding Flat, but ...
At 1999 Level After Adjusting for Inflation

Data provided by:
Mala Dutta, Ph.D.
Office of Translational Research, NEI
Total VC vs Biotech vs Device Investments (2001-2015)

Most Dramatic Increases NOT Biotech or Devices

Source: PricewaterhouseCoopers, Silicon Valley Bank

Courtesy Jon Norris
Lifescience Venture Capital Invested (2005 – 2014)

Invested ($Bn)

$6.0
$7.3
$9.1
$8.6
$6.6
$7.7
$6.7
$6.7
$8.6
$8.6


Source: PricewaterhouseCoopers, Silicon Valley Bank

But, Biotech and Devices Also up ~ 30%

Courtesy Jon Norris
Ophthalmic Investments Over Time (1999 – 2015*)

Ophthalmic VC Funding Stable Overall
~ $400 - 500M / year

*2015 figures through October

SOURCE: Strategic Transactions
NEI Funding
Comparable to VC, but Modest in Comparison to Industry at Large

<table>
<thead>
<tr>
<th></th>
<th>2009</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcon</td>
<td>~ $670M</td>
<td>~1Bn</td>
</tr>
<tr>
<td>VC</td>
<td>~ $380M</td>
<td>~$500M</td>
</tr>
<tr>
<td>NEI</td>
<td>~ $665M</td>
<td>~$676M</td>
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</tbody>
</table>

**INNOVATION IN RETINA**

A “Tipping Point” for Retina R&D: Implications and Expectations

PRAVIN U. DUGEL, MD • EMMETT T. CUNNINGHAM, JR., MD, PHD, MPH

**RETIINAL PHYSICIAN | SEPTEMBER 2010**

**Total Funds Invested in Ophthalmic Research and Development, 1999 - 2009**

- **NEI**
- **VC**
- **Alcon**

**Allergan**

Genentech
A Member of the Roche Group

**Regeneron**

science to medicine®

**Shire**

abbvie

**Valeant Pharmaceuticals International**

**Bausch + Lomb**

See better. Live better.

**etc...**
Translational Research

- Laboratory Research
- Clinical Research
- Treatments

Early Stage VCs → Late Stage VCs

SBIR

Industry
Understand Funding Sources / Risks

### Stage
- Pre-Seed
- Seed / Startup
- Early
- Late

### Source Of Funds
- Founders
- Friends
- Family
- SBIR / Foundations
- Angels / Incubators
- Institutional Investors (VC)

### Funds Required
- $50K
- $100K
- $1M
- $100M

### Availability Of Funds
- “Innovation Gap”

### Risk
- High
- Low

Risk Not drawn to scale!

Modified after: Center for Venture Research – University of New Hampshire
VC Investment By Ophthalmic Indication (1999-2015*)

*2015 figures through October
SOURCE: Strategic Transactions
2 – Retina

Enhanced Efficacy Through Improved Compliance
(Sustained Release & Gene Therapy)
Global Causes of Blindness
World Health Organization - 2010

- Undetermined: 21%
- Cataract: 51%
- Retina - 6% and growing
- Diabetic Retinopathy: 1%
- Trachoma: 3%
- Refractive Error: 3%
- Childhood: 4%
- Corneal Opacity: 4%
- AMD: 5%
- Glaucoma: 8%

http://www.who.int/blindness/data_maps/en/
Global Ophthalmic Procedures - 2015

- Vitrectomies
- Laser Photocoagulation
- IVT Injections
- Cataract, RLE, Phakic IOLs
- Glaucoma Filtering, Shunts, MIGs
- Laser Refractive
- Glaucoma Laser
- All Other
- Laser Photocoagulation
- Retina – 25.7M
- Cataract, RLE, Phakic IOLs – 24.2M

Global Ophthalmic Pharmaceutical Market
Revenues by Indication

<table>
<thead>
<tr>
<th>Indication</th>
<th>2015</th>
<th>2020</th>
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<tbody>
<tr>
<td>Glaucoma</td>
<td>9.3</td>
<td>16.5</td>
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<tr>
<td>Dry Eye</td>
<td>4.7</td>
<td>6.1</td>
</tr>
<tr>
<td>Anti-VEGF/Retina</td>
<td>3.1</td>
<td>3.7</td>
</tr>
<tr>
<td>All Other</td>
<td>3.8</td>
<td>4.2</td>
</tr>
<tr>
<td>Total</td>
<td>$20.9Bn</td>
<td>$30.5Bn</td>
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Sustained-Release Corticosteroids

- Triesence (triamcinolone acetonide injectable suspension) 40 mg/mL
- KENALOG®-40 (triamcinolone acetonide injectable suspension, USP) 40 mg/mL
- Ozurdex intravitreal implant in applicator (dexamethasone) 700 micrograms
- Retisert (fluocinolone acetonide intravitreal implant) 0.59 mg
IVT α-VEGF Injections....

Courtesy Dr. Peter Karth and Dr. Marc Blumenkranz
Global IVT α – VEGF Injections


Most Growth OUS
Anti-VEGF for nAMD, DME, RVO
US Retina Specialist Treatment for Wet AMD

Source: Market Scope Estimates; Courtesy Dave Harmon. [http://market-scope.com/]
Clinical Monitoring of Patients With Age-Related Macular Degeneration Treated With Intravitreal Bevacizumab or Ranibizumab

Szilárd Kiss, MD; Ying Liu, PhD; Joseph Brown, MBA; Nancy M. Holekamp, MD; Arghavan Almony, MD; Joanna Campbell, PhD; Jonathan W. Kowalski, PharmD. MS


A

**Bevacizumab**

Mean number of injections: 5.3

B

**Ranibizumab**

Mean number of injections: 6.8
Clinical Utilization of Anti-VEGF Agents and Disease Monitoring in Neovascular Age-Related Macular Degeneration

NANCY M. HOKEKAMP, YING LIU, WEI-SHI YEH, YIFENG CHIA, SZILÁRD KISS, ARGHAVAN ALMONY, AND JONATHAN W. KOWALSKI


Strong Correlation Between Injection Frequency and Vision Gain

Study-Enforced Compliance Results in 4-5 Letter Mean Gain – As Much As Effective Add-On Therapy
Sustained Release For Posterior Segment

Phase 2b 2Q2015

Simultaneous Detection of Chemokines, Cytokines, Growth Factors (eg, VEGF)

Free Drug Release As Particles Erode

Pre-IND

Pre-IND Replenish Micropump™
Ranibizumab (RBZ) Port Delivery System (RPDS)
For Wet AMD – LADDER Trial

Phase 2 multicenter, randomized, interventional, active treatment-controlled study
Wet AMD population (N = 220)
Randomized 3:3:3:2
- RPDS Implant RBZ formulation 1 N=60
- RPDS Implant RBZ formulation 2 N=60
- RPDS Implant RBZ formulation 3 N=60
- ITV SOC RBZ 0.5 mg/ml Monthly N=40

Phase 2 Data 1H2017

Gene Therapy in Ophthalmology
At the Tipping Point?
Positive Phase 3 Trial of SPK-RPE65 for the treatment of RPE65-mediated inherited retinal dystrophies (IRDs).
BLA Submission 2016

*As measured by the change in bilateral mobility testing between baseline and one year. The multicenter, pivotal Phase 3 trial randomized 31 subjects with confirmed RPE65 gene mutations. The ITT population included 21 subjects in the intervention group and 10 in the control group.

Phase 2 Data
Anticipated 2016

X-linked retinoschisis (XLRS)

http://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/XLRS.htm
3 – Glaucoma

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Glaucoma – 8%

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Global Ophthalmic Procedures - 2015

2.8M

- Glaucoma Filtering, Shunts, MIGs
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- Glaucoma Laser
- All Other
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Adherence Poor
(<50% by 6 months for most gtts)

2x higher with once daily therapy (prostaglandins) – still low
1234 Eligible Beneficiaries

A Minority had “Good Adherence” Over Time

• 20% at 1 year
• 15% at 4 years
Sustained Release Drugs for Glaucoma

Intracameral
Bimatoprost SR – P3

Mati Therapeutics Inc.

Latanaprost – P2

Punctal Plug

Helios™ Insert
Travoprost – P2

Ocular Therapeutix

Punctal Plug
Travoprost – P2
“iStent” - Approved for Glaucoma Surgery
June, 2012
CyPass® Micro-Stent
PMA Submission
Accepted by FDA
October, 2015

“Pivotal COMPASS Trial Results Positive through Two Years”

A Number of Followers in Clinical Development ...

INNFOCUS

MicroShunt

AQUESYS

XEN Glaucoma Implant

Hydrus Microstent

IVANTIS
US Glaucoma Surgical Procedures (000)

All Growth in MIGS In US

> 450,000

Global Glaucoma Surgical Procedures (000)

All Growth in MIGS Globally

> 900,000

4 – Cataract
Pharmaceutical Treatment
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Cataract, RLE, Phakic IOLs

22.2M

“Sterol eye drops reverse cataracts in mice”
Sterols target crystallin to restore lens transparency in mouse models of cataracts

c29 binds and stabilizes the dimer of cryAB to reverse aggregation

Slit lamp biomicroscopy photographs from R120G cryAB mice dosed topically with c29 eyedrops

www.viewpointtherapeutics.com
Centers of Innovation
An Eye on India and China

1.3 Bn

1.4 Bn
“Necessity may be the mother in invention”*

BUT

“Prosperity is the father of innovation.....”

A strong and sustained culture of innovation is predicated upon a strong economy with real or perceived discretionary spending...

*“...let us begin and create in idea a State; and yet a true creator is necessity, which is the mother of our invention.”

The Republic, Book II, 369c, Plato
Global Contribution to World's GDP by Major Economies from 1 AD to 2003 AD

Projected Relative Global Economies
2011 – 2030 - 2060

Note: Global GDP is taken as the sum of GDP for 34 OECD and 8 non-OECD G20 countries. Source: Johansson, Å., et al. (2012), OECD Economic Policy Papers, No. 3.
Figure 3: Comparison of FDA-approved drug and vaccine candidates (1995 to April 2011) compared with the innovation pipelines of domestic firms from China, India and Brazil and product breakdown based on nature of active substance.
An Eye on India and China

Emerging as Centers of Innovation

Intas Pharmaceuticals Launches Razumab ‘Similar’ to Ranabizumab

Kanghong Biotech Launches Combercept ‘Similar’ to Afilbercept

Sun Pharma Acquires Insight - $48M
Opinions May Vary ...