Discovery of Innovative Medicines: A Global Perspective

- My Healthcare Journey: **Lessons Learned**
- Drug Discovery in China
- Pipeline and Platform Opportunities
- The Healthcare Ecosystem

Lee E. Babiss
CEO, X-Rx Inc.
N.Y., N.Y.,

My View of Global Drug Discovery

It is a great time to Discover New Medicines

- Regulatory environments across the world are very favorable
- Novel Therapeutics Modalities are being validated
- Breadth of disease indications continues to grow
- Biotech's are partnering early drug candidates with Pharma
- VC landscape is strong
- Access to Capital has never been better
- Virtual/Fully integrated Biotech models have been validated
- CRO market is growing, but margins remain an issue
- Entrepreneurial Spirit, Talent and Creativity is great

With some challenges

- Patient access to breakthrough therapeutics
- Balance between safety and efficacy
- Disconnect between Discovery & Clinical
- Academic Drug Discovery

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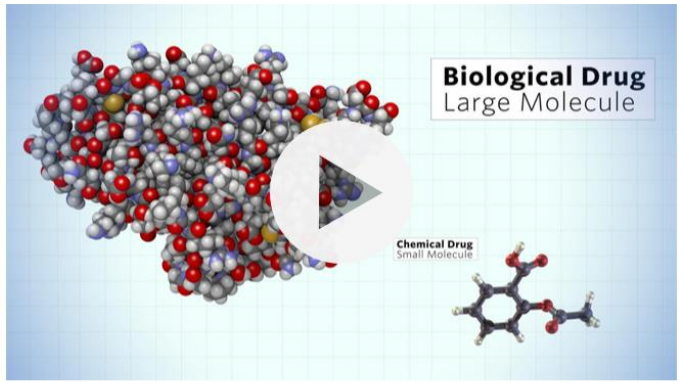
THE WALL STREET JOURNAL. AA

BUSINESS

China Emerges as Powerhouse for Biotech Drugs

Global drugmakers join with local Chinese startups to test and create new cancer treatments



By Preetika Rana

April 10, 2017, 10:53 am ET

SUZHOU, China—A new cancer drug li-

NEXT UP IN FOR YOU

What does the mean?

- Focus on Me Too
- Focus on Me Better
- Focus on Generics
- Focus on First in Class

Me Too is a good opportunity, as Pharma want access to proprietary drugs for polytherapy testing

Me Better can be a tough road, unless there are clear liabilities that can be addressed

Generics are no longer a good opportunity

First-in-Class, just starting to emerge and with great support

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My Personal Drug Discovery Journey

ACADEMIA	PHARMA	PHARMA	CRO	BIOTECH	VC	BOARDS

What experience do you want in the Drug Discovery Ecosystem?
My journey has opened the door for me to continue to learn and to be very marketable
It is very important to have a Broad understanding and expertise spanning the entire Value-Chain

Lessons Learned

1. You are an expert in one area
2. You work hard to become a semi-expert in many areas
3. You cannot succeed by working in isolation
4. The discovery of a new medicine requires a team approach
5. You can never take shortcuts
6. You must have the courage to take risk
7. You must learn when it is time to walkaway
8. You must learn by success and not by failure
9. You must lead by example & recognize teams and individuals

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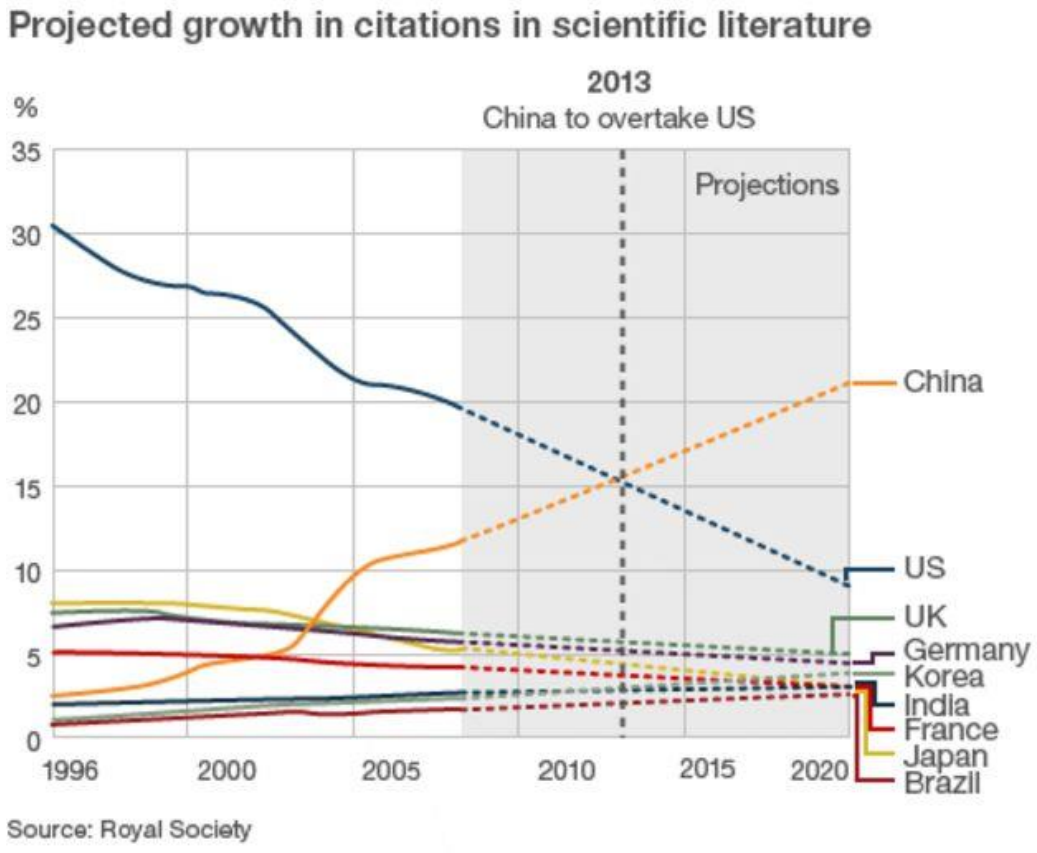
In the early days of Pharma R&D Centers in China

1. Support for the main R&D sites
2. Focus on indications in China
3. Getting approved drugs on Market

What is the reality?



- China education systems promotes STEM and provides funding
- Superb internal and returnee talent
- Publications are increasing and driven by significant internal pressure
- Many questions regarding Quality vs. Quantity….reproducibility of data?
- How does this equate to Drug Discovery?

Current	Proposed Changes	Savings
3x manufacturing for China trials and NDA has to be done in China	Manufacturing no longer has to be in China	~1 year $MM's
China IND approval required for clinical trial in China	Foreign-approved IND exempt from filing new IND request in China (*i.e.* adding a China arm to a global clinical trial)	~2 years or more for China IND approval
Need Phase 1 data from another country before doing trial in China	Foreign Phase 1 data not require a Chinese clinical trial	~1-2 years
China NDA requires Chinese clinical trials	Global clinical trials with a China arm required, but not a China-specific trial	~1-2 years
China IND approval very slow	IND/CTA approvals for drugs for certain indications such as cancer can start clinical trials within 3 months	~1-2 years

My Assessment of the Pharma/Biotech Market in China

1. China is no longer a small fish in a big pond
2. China has the talent, with some gaps in areas of drug discovery
3. Was the investment by Multi-National Pharma a success?
4. The entrepreneurial Spirit is high
5. Strong support from both local and Central Government and Global Venture Capital
6. Timelines for return on investment by investors is becoming more reasonable
7. Kick-starting new companies is now supported by in-licensing assets coupled with creative new starting points, over a broadening range of therapeutic modalities
8. No longer just about Generics and Me Toos
9. Small molecule screening platforms & COM

Navigating the Innovation Highway: Creating your Start Up Niche

Platform

- Exclusive
- Partnered
- Disruptive
- NextGen investment
- Growth
- Exit?

Information

- Personalized Healthcare
- Biomarkers
- Patient/Disease Stratification

Pipeline

- First in Class
- Best in Class
- Me too
- Disease, Pathway, Target family, Geographic focus
- Out-/in-license
- Platform access
- Endgame
- Exit?

The X-Rx Story

Concept

- Utilize the Power of Chemical Diversity to drug important targets that are deemed to be undrugable
- Fast and Efficient approach to achieve pre-IND drug candidates
- Management model that is Virtual, with only 4 FTEs, none of whom are co-localized
- Wet-lab efforts driven by working with the best CROs

Status

- In 2 years, we partnered our first program, Autotaxin for IPF, at the pre-GLP stage with Gilead Sciences
- In year 3, we partnered our second program, BTKi at pre-GLP with Synercare Pharma in China
- Currently we are advancing two programs into pre-GLP and are planning to take one of the programs into the Clinic….in discussions with several Pharma's

Learnings

- Virtual model has been validated and yields results in a rapid and cost-efficient manner with high Quality.
- Management Challenge requiring constant communication and Trust…eye on the Exit

RNA-Based Therapeutics: Validation?

Current Status of mRNA-& siRNA-based Therapeutics

Modified mRNA as the drug

- Seasonal Influenza
- Pandemic Flu
- CMV
- Zika

In the clinic as vaccine approaches, delivered by LNPs sc or IM and all meeting the clinical endpoints

Alnylam® PHARMACEUTICALS

siRNA as the drug and delivered by LNPs IM/sc

- PCSK9
- TTR

In the clinic and PCSK9 is ready for Ph3 and TTR had a safety issue, which has been resolved

Zika Overview

Rapidly emerging pandemic with potential long-term public health implications:

- Confirmed maternal / fetal and sexual transmission
- Flavivirus - like Dengue & Yellow Fever
- *Aedes* mosquito vector like Chikungunya

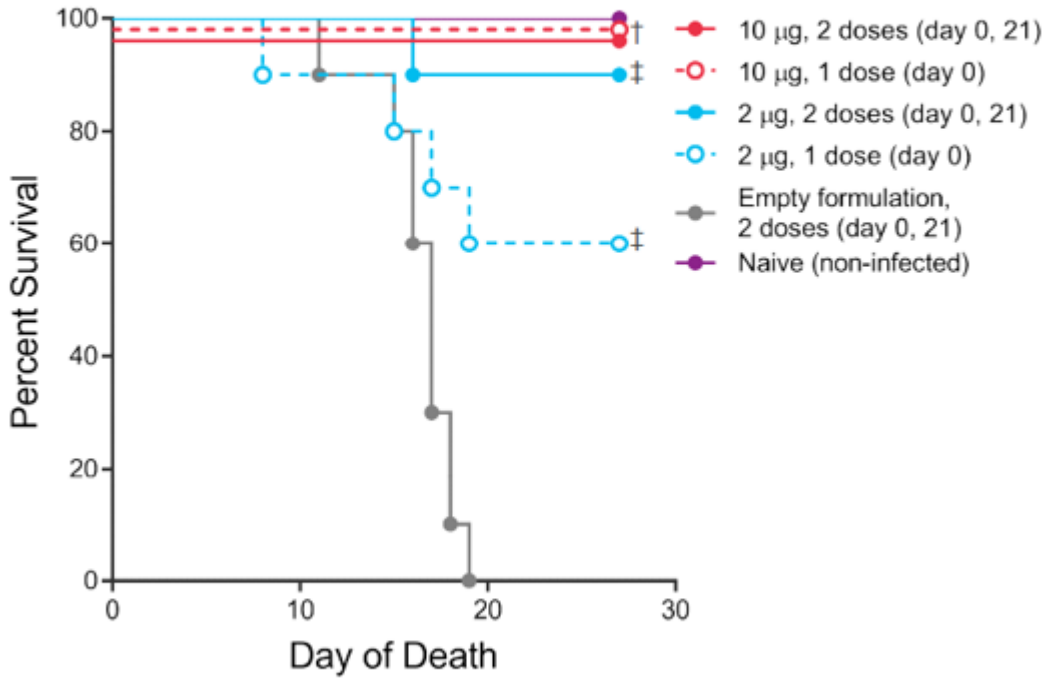
Causal link to at least two diseases:

- Microcephaly
- Guillain-Barré Syndrome (GBS)

- Modified mRNA to enhance translation/protein production
- Minimize an active innate immune response

Study Design:

- AG129 mice dosed with mRNA-1325 (n=10 animals/group)
- Prime (day 0) or prime-boost (days 0, 21)
- Challenged with 100pfu of Malaysian strain at day 42



†10 µg provided 100% protection, even with a single dose.

‡2 µg provided 90% protection; 1 dose provided 60%.

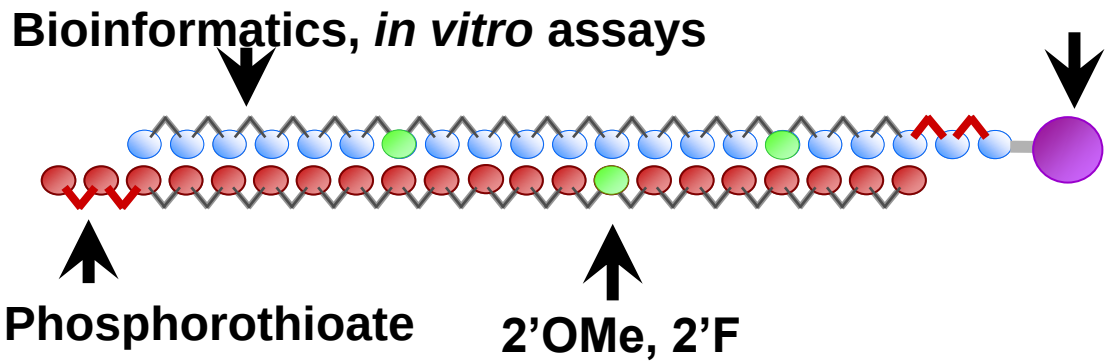
Is mRNA as a drug now a “Validated Therapeutic Modality”?

- LNP/VLP delivery of mRNA has been validated
- Targeting of tumors and other organs has not yet been validated
- Huge potential in the following areas:
  - Vaccines
  - ImmunoOncology
  - Rare Diseases

But not a generalizable platform yet…..

Therapeutic siRNAs:

Success Targeting the Liver

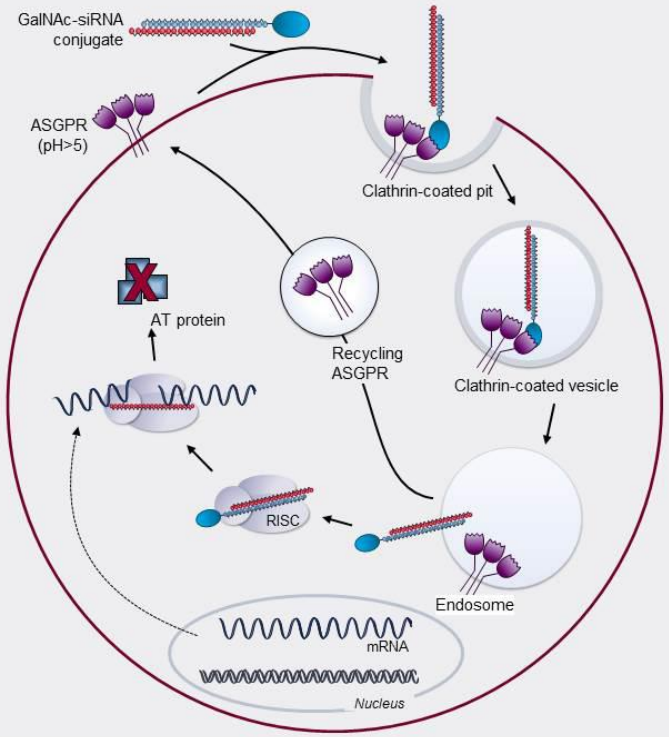


GalNAc-siRNA

- GalNAc ligand conjugated to chemically modified siRNA to mediate targeted delivery
- Trivalent GalNAc carbohydrate cluster has nM affinity for ASGPR
- Subcutaneous administration

Asialoglycoprotein Receptor (ASGPR)

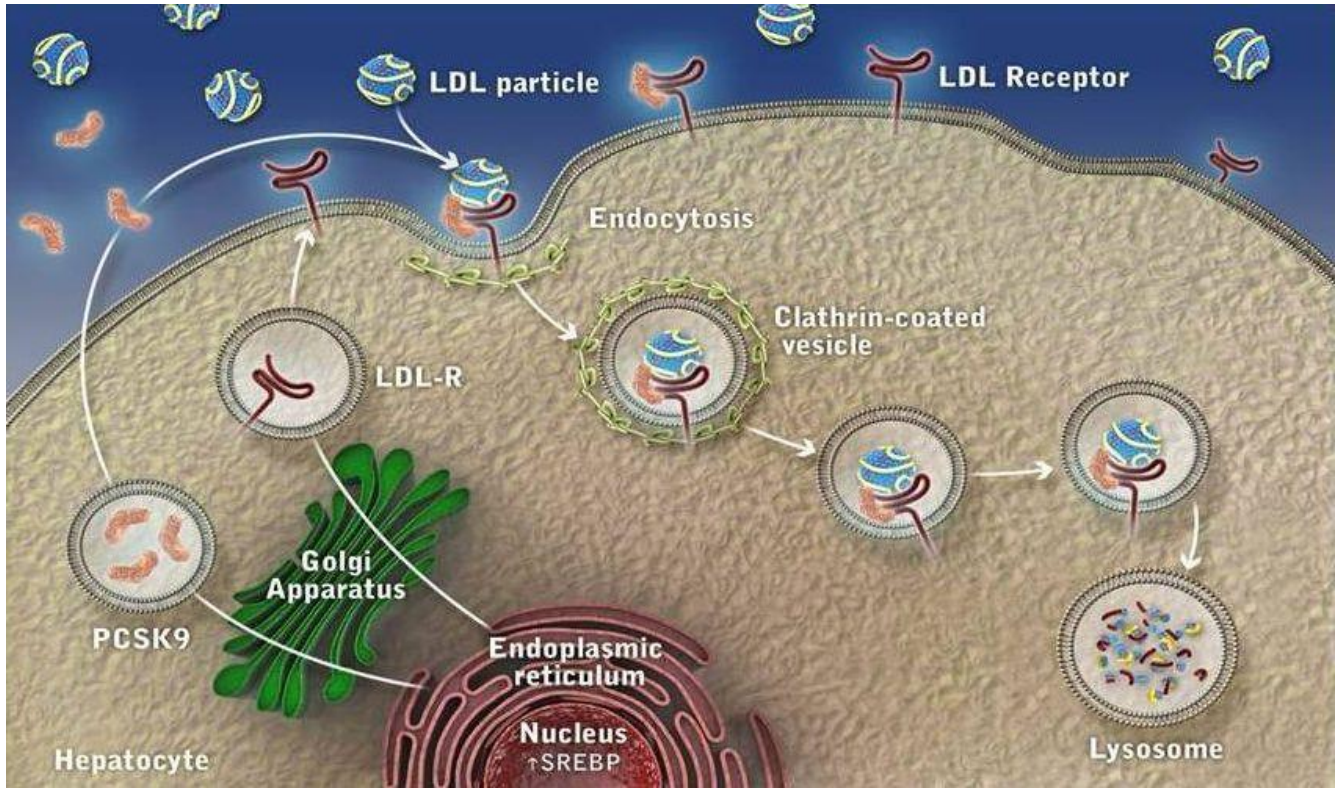
- Clears serum glycoproteins via clathrin-mediated endocytosis
- Well suited for receptor-mediated, targeted delivery
- Conserved across species



PCSK9 Program: POC for liver and MOA

<u>Proprotein convertase subtilsin/kexin type 9 (PCSK9)</u>:

- Binds to EGF-A like domain of LDLR, targets LDLR for degradation



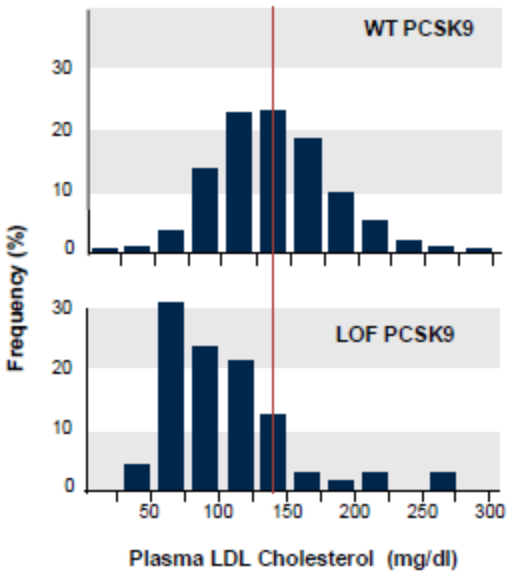
PCSK9

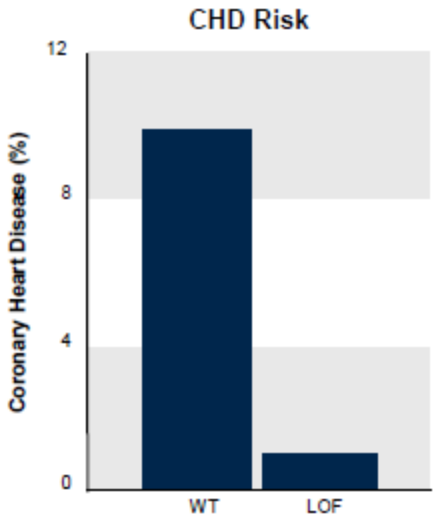
Unmet need in hypercholesterolemia

- Elevated LDL-C validated risk factor for coronary heart disease (CHD)
- 34 million Americans have hypercholesterolemia (> 240 mg/dL)
- Recent clinical studies
  - Many patients on statins do not meet LDL-C goal
  - Lower LDL-C is better (IMPROVE-IT)
- Multiple genetically defined patient subgroups

PCSK9 is genetically validated target

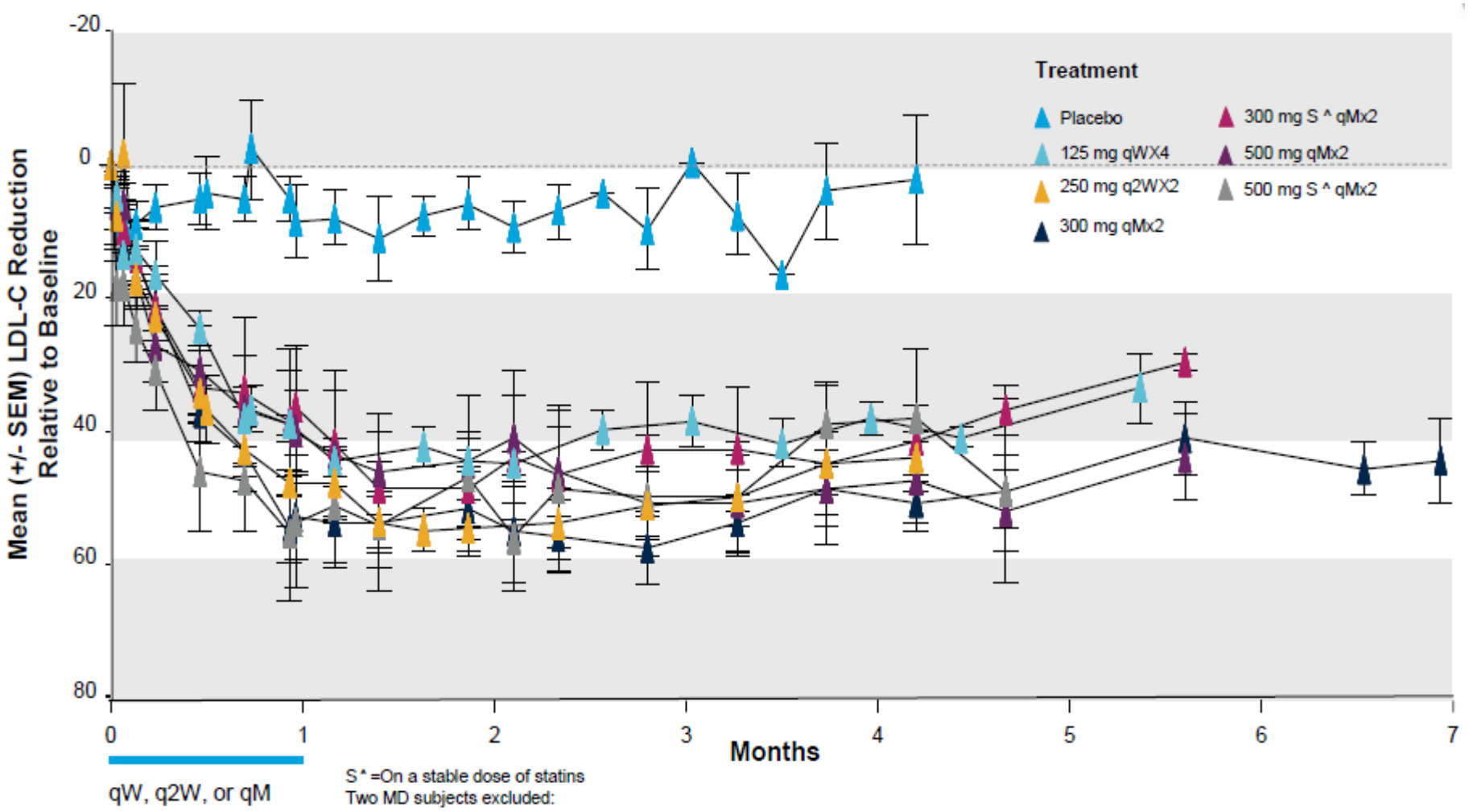
- GOF mutations associated with hypercholesterolemia and premature CHD
- LOF mutations associated with hypocholesterolemia and decreased CHD risk





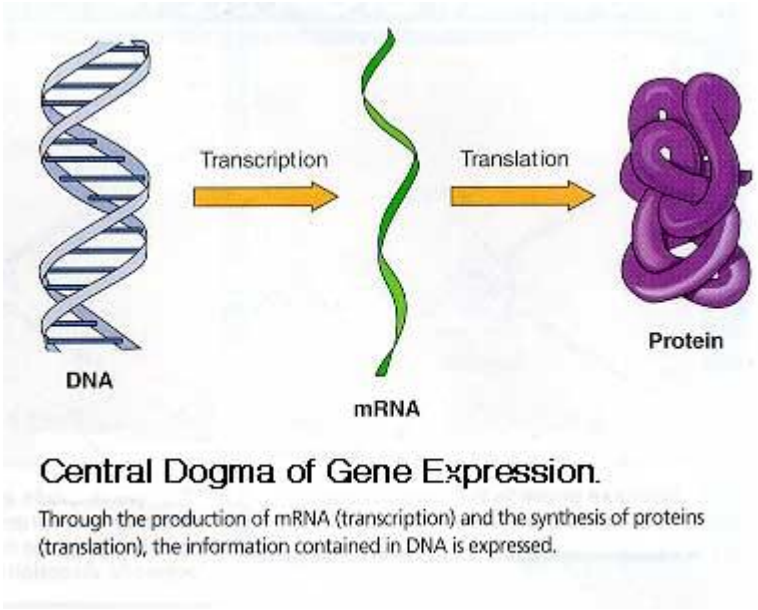
Pearson *et al.*, L-TAP Study, *Arch Intern Med*; 160:459-67 (2005),
Blazing *e al Am. Heart J*; 168:205 (2014)
Cohen *et al., N. Engl. J. Med.*; 354:1264-1272 (2006)

Initial Phase 1 Study Results
LDL-C Lowering Relative to Baseline



Max LDL-C reduction of 83.0% with mean max of 64.4 ± 5.4%

Central Dogma of Molecular Biology



Central Dogma of Gene Expression.

Through the production of mRNA (transcription) and the synthesis of proteins (translation), the information contained in DNA is expressed.

Are All mRNAs created equal? NO!!!!

- **mRNAs display plasticity driven by**:
  a. Alternative Splicing
  b. Alternative Nucleosides
  c. Differential m6A/m6Am methylation
  d. miRNA regulation of translation
  e. Modified nucleosides
  f. Cap-dep and Cap-indep translation
  g. lncRNAs

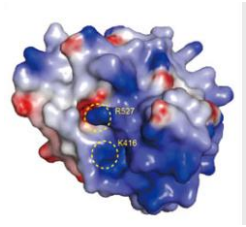
- **Is there a causal role for mRNA modifying proteins in human diseases?**
- **Can we create small molecule drugs that target mRNAs and in so doing derive therapeutic outcomes?**

m6A methylation of mRNA is dynamic and regulates mRNA metabolism & function : First noted in the 1960's?

The Cast of Characters: Which should be drugged?

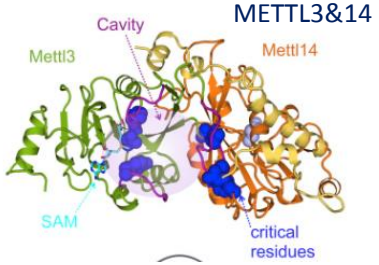
Readers
Transcripts containing m6A's are recognized and regulated by reader proteins, such as cytoplasmic YTHDF2 (destabilizes mRNA) and nuclear YTHDC1 (modulates pre-RNA splicing)

YTHDF2



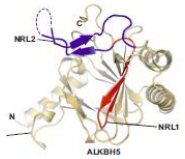
Writers
m6A methylation is catalyzed by a multiprotein complex containing the METTL3 & METTL14(drives mRNA methylation) and with WTAP (enhances methylation and nuclear localization of the METTL heterodimer) Structure determined

METTL3&14

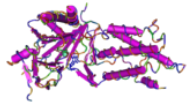


Erasers
ALKBH5 & FTO are mammalian demethylases that oxidatively reverses m(6)A in mRNA. This activity curbs mRNA export and RNA metabolism as well as the assembly of mRNA processing factors in nuclear speckles. Upregulated in several cancer types and metabolic disorders. Structure determined.

ALKBH5

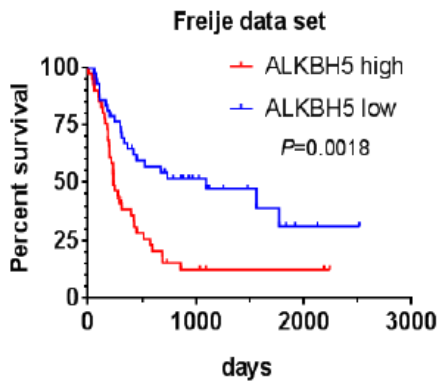


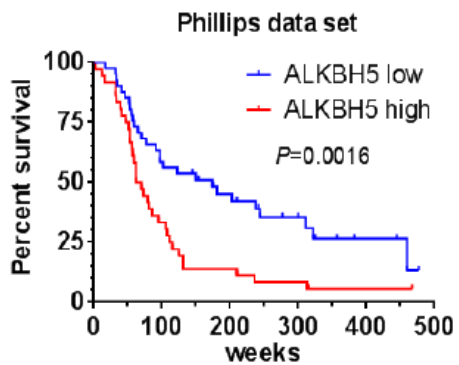
FTO

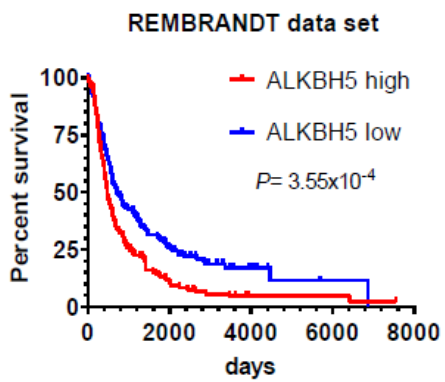


m6A abnormalities are linked to cancer: ALKBH5 overexpression **Prognostic vs. Therapeutic**

- ALKBH5 is normally expressed primarily in testes; KO mice are normal except for altered sperm development
- Breast cancer: Elevated ALKBH5 implicated in breast cancer especially in hypoxic cancers (Zhang et al., PNAS, 2015; Zhang et al., Oncotarget, 2016). Pluripotency gene induction by hypoxia is mediated by ALKBH5. ALKBH5 knockdown impairs tumor formation, metastasis and breast cancer stem cell formation.
- Prostate cancer: Large study of prostate cancer outcomes (n = 430) identified ALKBH5 as one of five top markers for predicting metastatic-lethal prostate cancer vs. non-recurrent prostate cancer (Zhao et al., Clin. Cancer Res., 2016)
- Glioblastoma: Poor prognosis in ALKBH5 positive glioma. Overall, ALKBH5 elevation is associated with poor prognosis in diverse cancers.







Will this be the next therapeutic mRNA platform?

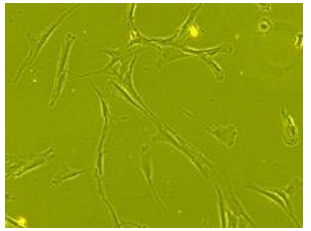
Cell-Based Therapeutics…An Emerging Validated Platform?

What are Mesenchymal Stem Stems?

- Multipotent Stromal cells that can differentiate into a variety of cell types.
- MSCs have a great capacity for self-renewal while maintaining their multipotency
- Can be isolated from Bone Marrow, Adipose Tissue, placenta, Liver, etc.
- MSCs avoid allorecognition, interfere with dendritic cells and T-cell function, and generate a local immunosuppressive microenvironment by secreting cytokines
- MSCs have been shown to home in on areas in the body that experience damage and they drive a corresponding immune response, to dampen such

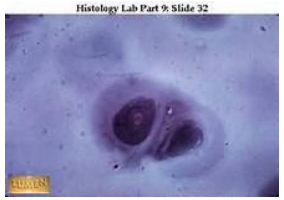
Can the addition of MSCs blunt perfusion injury associated with Ischemic Stroke?

MSC

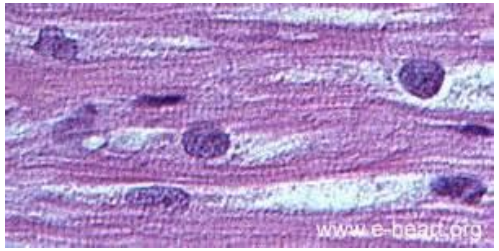


Osteoblast

Chondrocyte



Myocytes



Adipocytes

How Serious Is Stroke?

- About 700,000 strokes occur each year in U.S..
- Over 167,000 deaths each year.
- #3 killer.
- A leading cause of serious long-term disability in adults.
- 4.7 million stroke survivors.
- Number of cases growing rapidly in China and care is poor
- Driven by Genetic Risks, High fat diet and inactivity

U.S. Stroke Belt

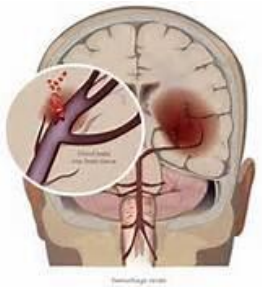
Very High Costs to support Stroke Survivors

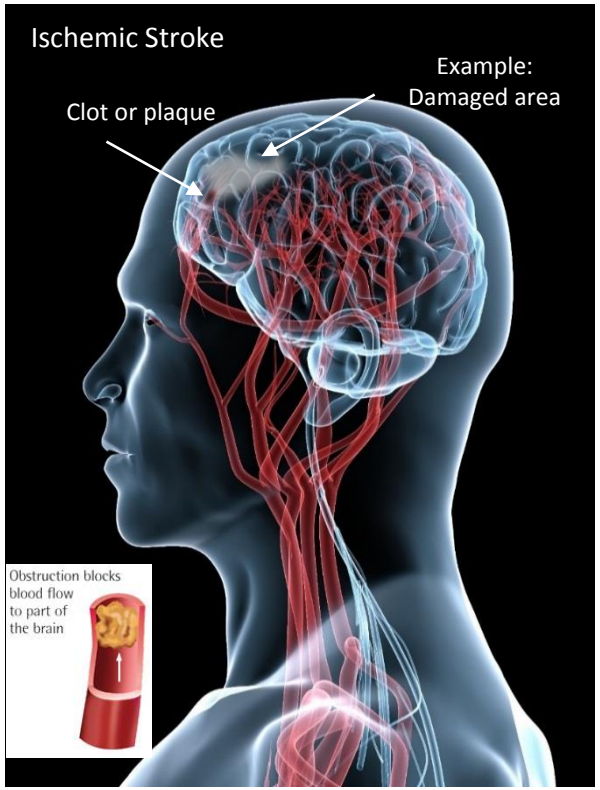
Classification of Stroke

<u>Two major categories:</u>

- Ischemic strokes, caused when a blood vessel supplying the brain is occluded Responsible for 75% of all strokes.
- Hemorrhagic strokes, caused when a cerebral artery ruptures.

Both forms are life threatening.





Drugs: *Fibrinolytic Therapy for Ischemic Stroke*

- Intravenous tPA represents the first FDA-approved therapy for acute ischemic stroke.

- In the NINDS trial, patients treated with tPA within 3 hours of onset of symptoms were at least 30% more likely to have minimal or no disability at 3 months compared with those treated with placebo.

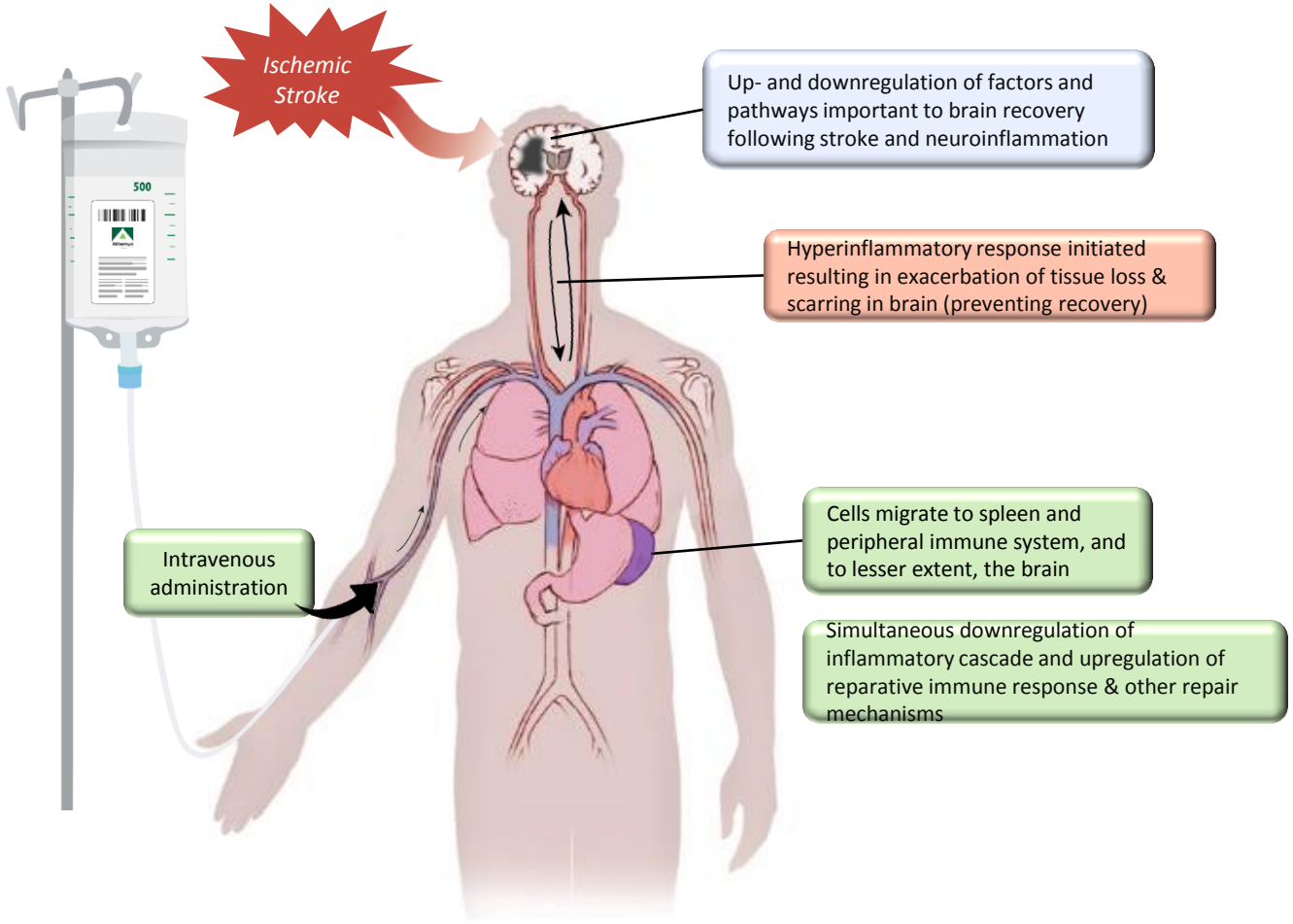
- In the U.S., 22% of all Ischemic Stroke Patients make it to an ER in 3hr and of these, only 22% are eligible for tPA starting at 4.5hr
- Recurrent Strokes/Ischemic events occur at a rate of 10-15% in the first 90 days

Better therapies are necessary given the increase in Strokes globally

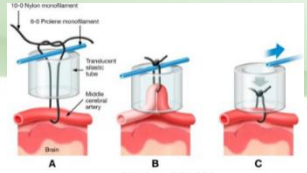
tPA Tissue Plasminogen Activator…only approved drug and dissolves the clot

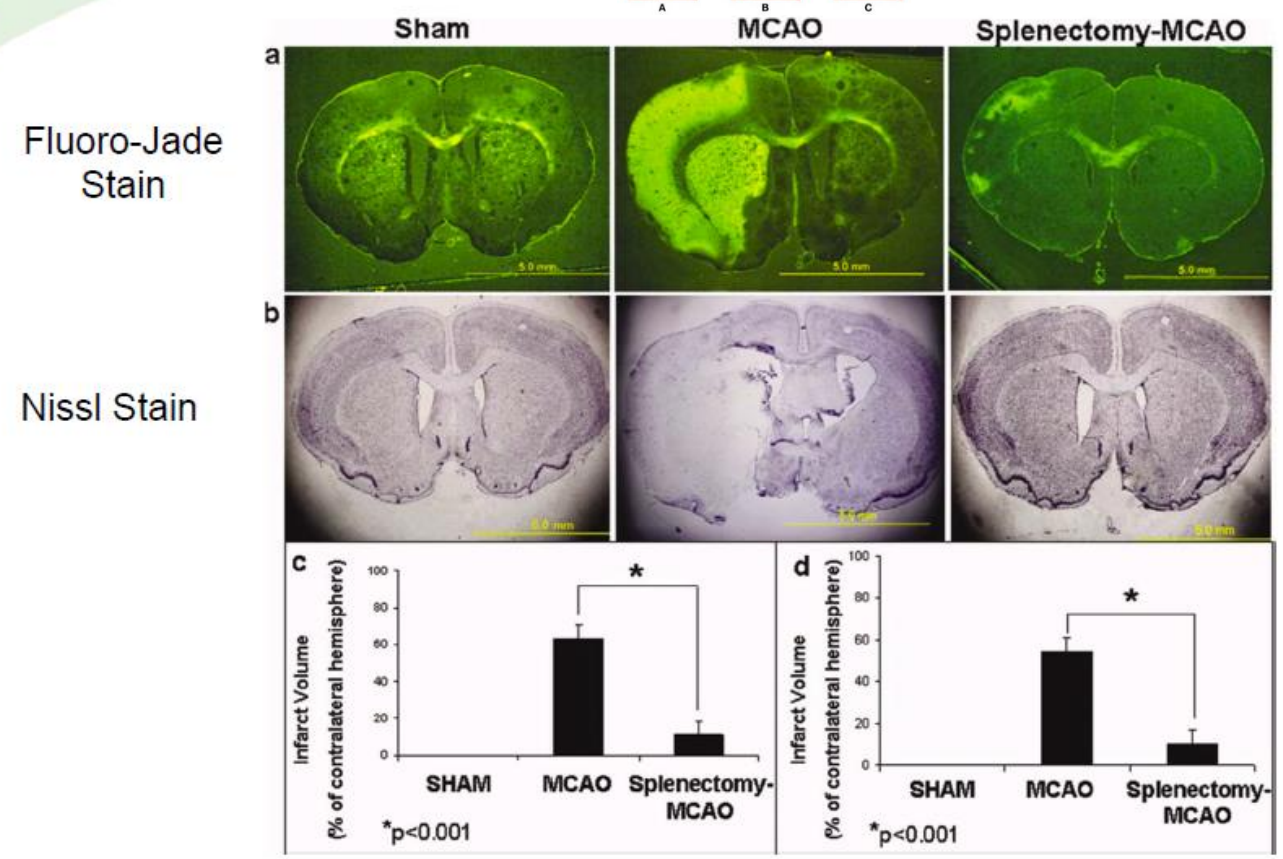
Why MultiStem for Stroke: How it works

Induction of Proinflammatory signaling pathways: INFγ, TNFα, IL1β, IL16, Tgfβ upregulated by Macrophages, microglia and astrocytes



Splenectomy Reduces Infarct Post-stroke



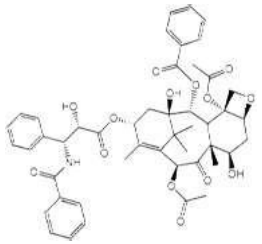


Ajmo et al., (2008). J Neurosci Research 86: 2227-2234.

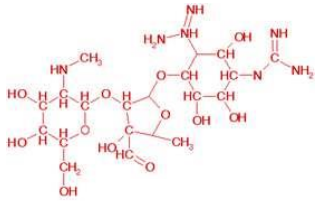
Multistem Impressive Phase II data with administration within 18-24hrs

Small Molecules
Ready for next quantum change?

Natural Products

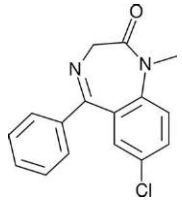


Taxol

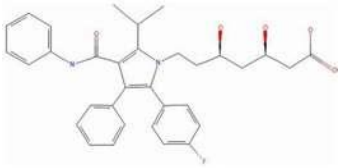


Streptomycin

Small Molecules

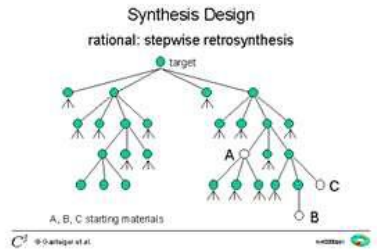


Valium

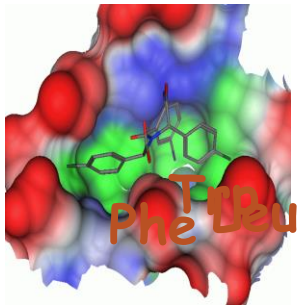


Lipitor

Libraries

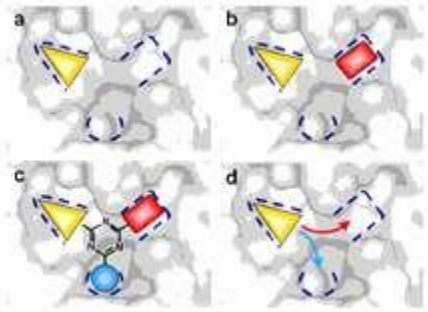


Structure-Based

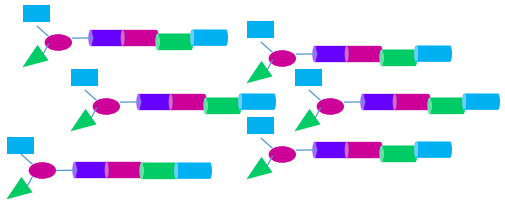


P53/mdm2

Fragment-Based



DNA Encoded Library



Progress, but still many issues to address

Platform Observations/Conclusions

- Many novel therapeutic modalities are progressing to being highly enabling and are and will become part of the mainstream of healthcare

- Such therapeutic modalities can uniquely address human diseases that were previously thought to not be addressable

- The impact of these new modalities is changing the practice of medicine to the point where medicines can be created to address;
  - Populations
  - Stratified forms of common diseases
  - Individualized therapies

- Finally the time from concept to market is shrinking and success is increasing
- Great opportunity to transition from Platform to Pipeline

CONVERGENCE IN HEALTHCARE

NGOs

Academia

Government

CROs

Foundations

Biotech

Pharma

Summary and Conclusions

- **The Healthcare Dynamics in China are Changing Rapidly**
  - **With a higher standard of living comes a heavy price to pay with high rates of Chronic Diseases**
  - **While QOL is improving, life-expectancy is lessening**

- **China recognizes these challenges and is investing heavily in:**
  - **Improving Healthcare and emergency responses throughout the Country**
  - **Investing heavily in improving the Healthcare infrastructure**
  - **Investing heavily in transitioning from Generics to First and Best in Class drug discovery and development capabilities (platforms)**
  - **Reducing Environmental Exposure**

- **China will greatly benefit by investing in the actions above**