

# LATE BREAKING TOPICS IN CARDIOLOGY

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# CARDIOVASCULAR DRUG ACTIVITY

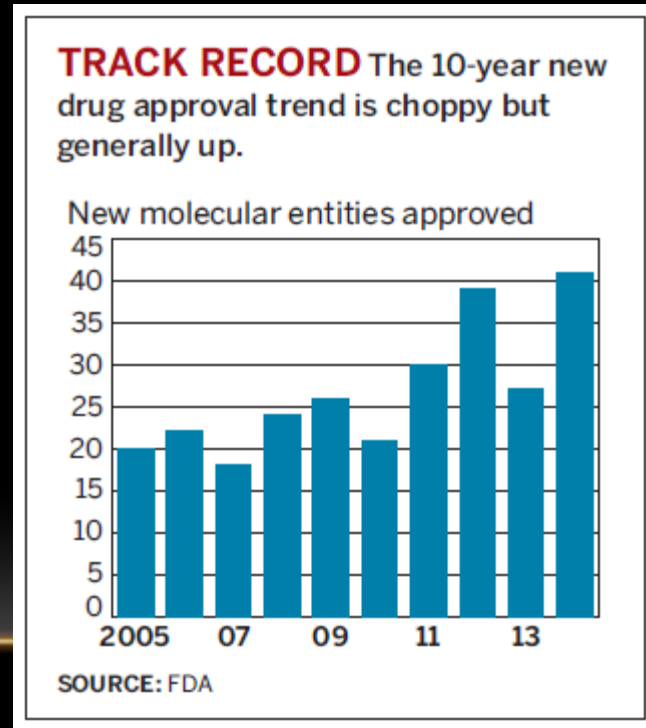
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# *FDA ACTIVITY FOR 2014 PEAKED IN TWENTY YEARS*

- The last 20 years have seen a dearth in drug development.
- The Food & Drug Administration's green light for 41 new molecular entities—the biggest crop in nearly two decades—signaled a return to innovation for an industry that just five years ago seemed stagnant.

# WHAT'S HAPPENING IN THE PHARMACEUTICAL INDUSTRY?

2014 was one for the record books despite sky-high merger and acquisition activity, there was unprecedented levels of financing.



# APPROVAL ROSTER

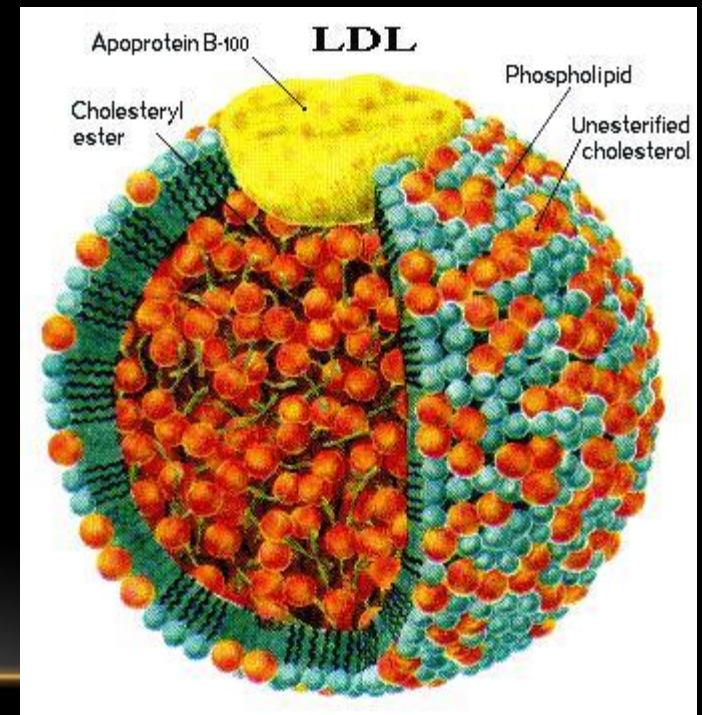
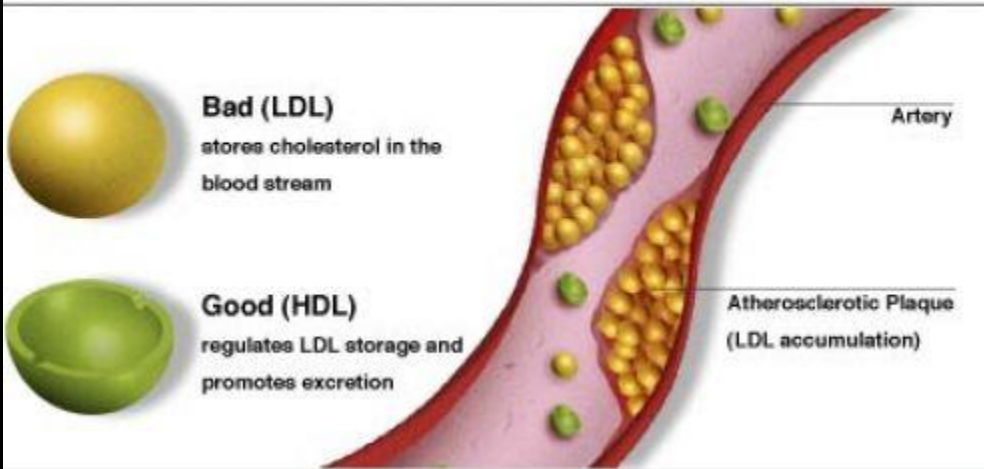
- 8 for Cancer
- 16 for “orphan” diseases
- 9 for infective disease
- 4 for diabetes
- 2 diagnostic imaging contrast
- 1 for COPD
- ONLY ONE FOR CV: Zontivity (vorapaxar) Merck & Co.  
PAR-1 antagonist -To reduce the risk of heart attacks and stroke

## *WHAT ABOUT NEXT YEAR?*

- Regulatory filings to date are still slow for a shift to cardiovascular:
  - Novartis - LCZ696 for heart failure (Diovan + neprilysin inhibitor Salubitril)
  - Amgen and Sanofi – PCSK 9 inhibitor for LDL lowering
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# NEW DRUG CLASS: PCSK9 INHIBITORS FOR CHOLESTEROL REDUCTION

## Bad vs. Good Cholesterol

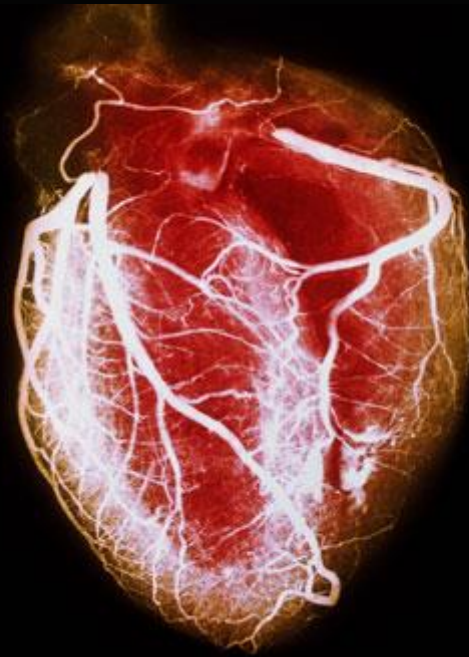


# *PCSK9 INHIBITORS FOR CHOLESTEROL REDUCTION*

- For two decades, doctors have reduced cholesterol with only statins has their primary choice.
  - Unfortunately, some patients are intolerant and cannot benefit from them.
  - In 2015, the FDA is expected to approve the first PCSK9 inhibitor, an injectable cholesterol lowering drug for patients who are statin intolerant.
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# NEW HEART FAILURE DRUG



## *ARNI FOR HEART FAILURE*

- The FDA has granted fast-track status to approve angiotensin-receptor neprilysin inhibitor (ARNI).
- Combines sacubitril, a neprilysin inhibitor, with angiotensin receptor blocker (ARB)
- ARNI has demonstrated a significant increase in the survival rate of heart failure patients when compared to those treated with the current standard medication, the ACE inhibitor enalapril.

# DEVICE ACTIVITY

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## *FDA APPROVED DEVICES FOR 2014*

- 41 devices were approved last year
- Of these 17 or 42% were cardiovascular
- Majority were:
  - Stents
  - Valves
  - Improvements to pacemakers

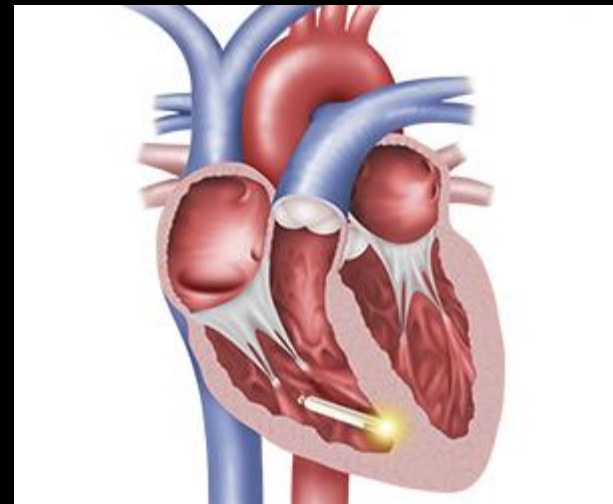
# WILL THIS BOOM CONTINUE?

- Medical device recalls have called attention to the device approval process in the United States.
- The premarket approval (PMA) process requires clinical trials to evaluate safety and effectiveness, the expedited 510(k) process does not. The 510(k) process has been considered a source of increased recalls.
  - There were 249 recalls due to serious risks, 0.45% of PMA approvals, and 0.92% of 510(k)-cleared devices,  $p < 0.001$ . Over 1/2 of the recalls were during the first 2 years on the market.
- Percentage of recalled PMA devices was unchanged over the 8 years, whereas 510(k) recalls increased in 2010 to 2012 (from 0.65% to 1.39%,  $p < 0.001$ ).
- Cardiovascular devices represent the largest class of recalls (27%).
- Modifying the 510(k) process with more rigorous performance testing, a conditional 2-year approval and a mandatory registry may be an approach to reduce recalls.

# ***IMPROVED CARDIAC PACEMAKER DESIGN – LEADLESS PACEMAKER***

- Artificial pacemakers have been surgically inserted into countless cardiac patients over the last half-century to regulate their heartbeats. The design has remained essentially the same, with a pulse generator transmitting electronic current to the heart via small wires inserted into a vein.
- Faulty or damaged wires lead to infections in 2% of cases.
- New pacemakers have been designed to be inserted directly into the heart itself. They are much smaller (about the size of a medication capsule) and can be implanted via minimally invasive surgery.

# *LEADLESS CARDIAC PACEMAKER*

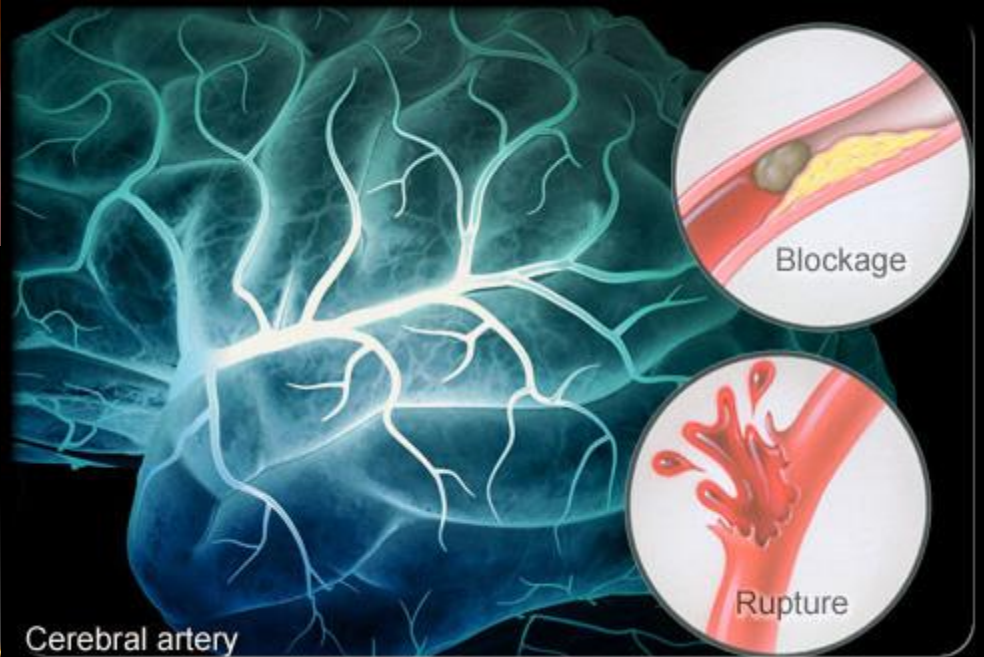


WHAT DOES THE FUTURE HOLD?

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# MOBILE STROKE UNITS



Cerebral artery

# *MOBILE STROKE UNITS*

- A mobile stroke unit is staffed with:
    - a paramedic
    - a critical care nurse
    - a computerized axial tomography (CAT scan) technologist
  - Neurological function is evaluated
  - tissue plasminogen activator (t-PA) is quickly administered
  - Telemedicine allows specialized stroke neurologists at a hospital or other facility to consult via broadband video.
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# New Blood Draw method

- painless
- more accurate
- Faster
- less expensive



# *NEW BLOOD DRAW METHOD*

- Gone are the needles and vials, replaced instead by a proprietary software and hardware technology that uses but a drop of blood from the capillaries at the end of a finger in a virtually painless procedure. The blood sample is wicked into a special nanotainer, which holds the equivalent amount of a raindrop.

Shipped to a special CLIA-certified laboratory, hundreds of different tests can now be performed from that one drop of blood, from standard cholesterol checks to sophisticated genetic analyses.

Blood results are then sent back to the requesting physician in a matter of hours. When further testing is needed, it can be done immediately, again with the same tiny blood sample.

This testing can be collected at a local participating pharmacy as well as a doctor's office.

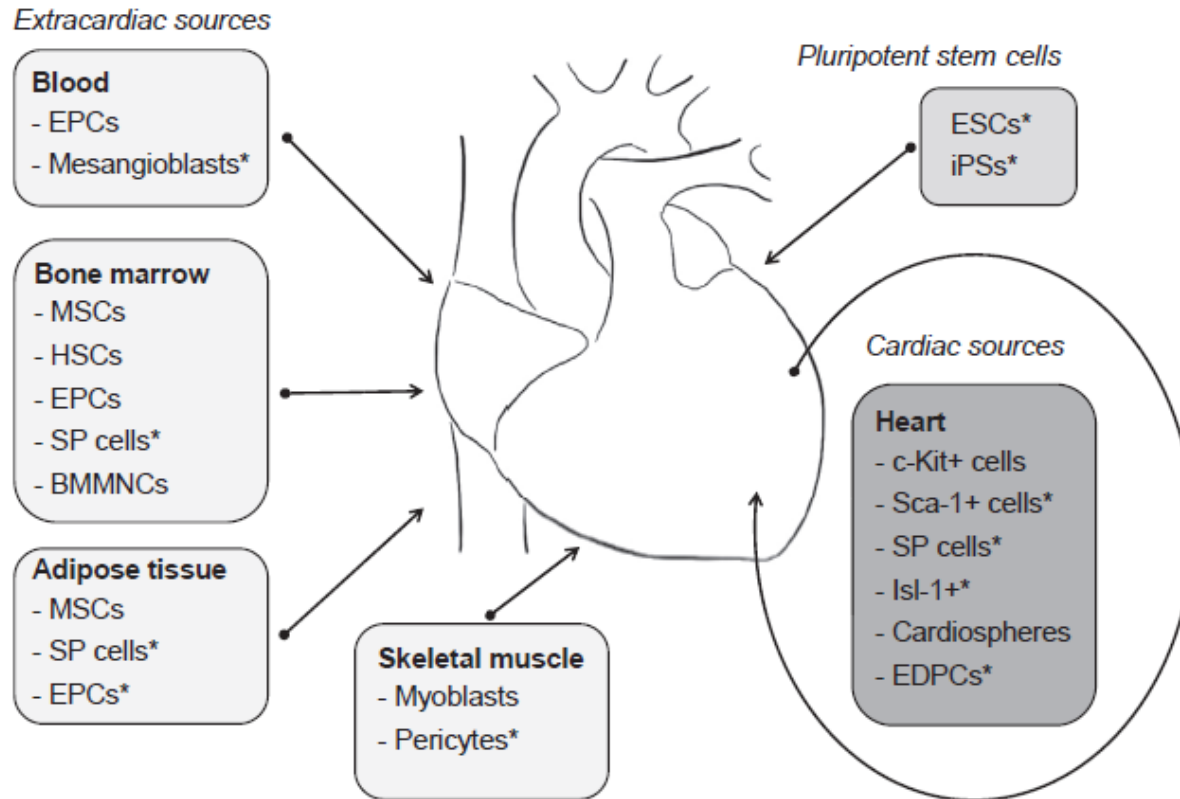
- These new tests will cost as little as 10 percent of the traditional Medicare reimbursement.

Where the cost of a standard lipid panel, one of the most common blood tests, is seemingly arbitrary and has varied wildly in price between \$10 and \$10,000 from hospital to hospital in this country, the new blood test will cost \$2.99.

# *CELL-BASED THERAPIES FOR CARDIOVASCULAR REGENERATION*

- Recent insights into myocardial biology has uncovered a unknown regenerative capacity of the adult heart.
- Discovery of dividing cardiomyocytes and the identification/characterization of cardiac stem and progenitor cells with myogenic and angiogenic potential have generated new hopes that cardiac regeneration and repair.
- Multiple candidate cells have been proposed for cardiac regeneration:
- Bone marrow-derived cells have yielded very mixed results
- Stem cells delivered into the myocardium act mainly via paracrine mechanisms yield a “slow” product.
- Cardiac committed cells (eg, resident cardiac progenitor cells or primed cardiogenic mesenchymal stem cells) showed promising results in first clinical pilot trials.

# CELL-BASED THERAPIES FOR CARDIOVASCULAR REGENERATION



# 3D PRINTING

- 3D printing is a process of making three dimensional solid objects from a digital file. The creation of a 3D printed object is achieved using additive processes. In an additive process an object is created by laying down successive layers of material until the entire object is created. Each of these layers can be seen as a thinly sliced horizontal cross-section of the eventual object.

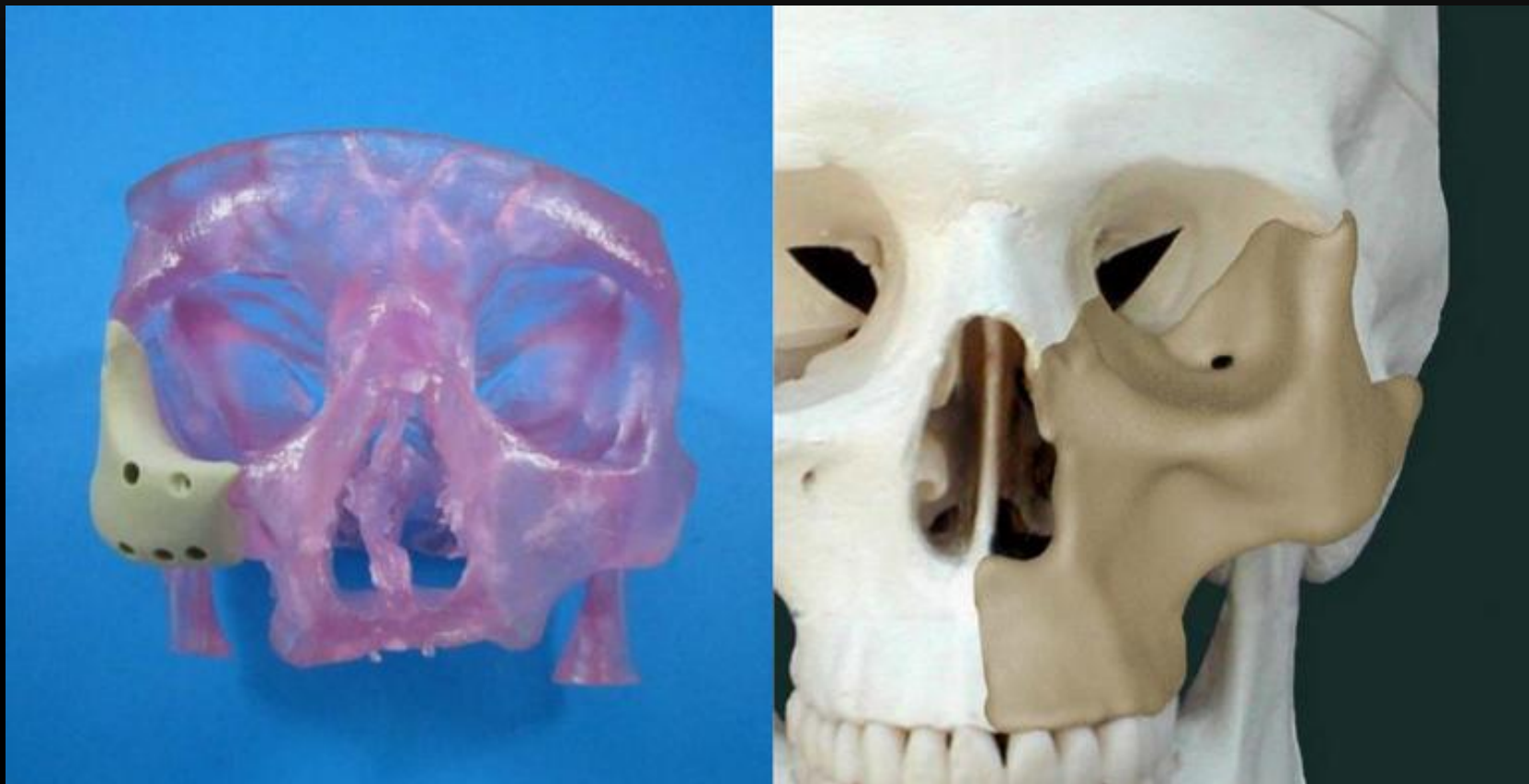


*WHY NOT COPY A HEART?*





# *FDA APPROVAL 3-D PRINTED FACE IMPLANT*



# BIOPRINTING

- The rapid prototyping process that is a means of patterning and assembling, layer by layer, functional living tissue, as well as nonliving substitutes for hard tissue, such as ceramic and titanium.
- Increasingly sophisticated bioprinters are becoming commercially available, and may be able to “print” complex cellular structures, such as human organs, directly into the human body.
- Bioprinters must have the ability to precisely place living material in 3-D space. This is usually realized with the help of a “robotic hand,” or X-Y-Z axis robotic precision positioning systems. Bioprinters must also have an automated syringe to facilitate
- the automated dispensing of living materials.
- Finally, printed tissue constructs must be collected in either a standard Petri dish or the more sophisticated chambers of a perfusion bioreactor.
- It has been demonstrated at the
- Medical University of South Carolina has fabricated an intra-organ branched vascular tree is possible. A bioprinted organ construct will not survive without it, so building a vascular tree is critically important.

# *ENVISIONTEC BIOPRINTER*



The 3D-Bioplotter from envisionTEC utilizes computer-aided design to engineer different types of tissue on a variety of scaffolding platforms. The scaffolds, which are constructed from a wide variety of materials ranging from collagen to titanium, help determine how the replacement tissue will grow.

# CONCLUSION

- New Cardiovascular drug development is not as productive as in the past.
  - While device research is at an all time high, increased regulatory restrictions due to past safety issues may slow development down.
  - Regenerative medicine is receiving much funding both at the academic and industry level.
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