A single combination gene therapy treats multiple age-related diseases

Ana-Cristina Rogoz

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University of Bucharest, Faculty of Mathematics and Computer Science

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Context

Context

This paper **focuses** on the following medical conditions:

- obesity,
- type II diabetes,
- heart and renal failure.

Draws attention about:

- the importance of extending one's health span,
- the increased risk of developing multiple medical conditions when the health span is over.

Context

It **develops AAV-based gene therapy** with the following genes:

- fibroblast growth factor 21 (FGF21),
- αKlotho,
- soluble form of mouse transforming growth factor-β receptor 2 (sTGFβ1).

Explores each therapy **individually** and in **combinations**.

Comes up with a formulation for treating **all four diseases**.

Personal motivation

Personal motivation

The addressed problem is **impactful**:

- People nowadays suffer from multiple diseases by the end of their life,
- Prescribed treatments ignore the interconnectedness of the involved diseases,
- There are multiple unanalyzed side-effects.

Introductory concepts

Gene therapy and AAV

Gene therapy - an **experimental approach**:

- may replace in the future the traditional treatments,
- to either alter a gene, overexpress, replace or introduce.

Adeno-associated virus is a:

- small, replication-defective, nonenveloped type of virus,
- virus not known to cause any disease,
- virus used in more than 100 medical trials.

AAV serotype

- AAV is **not able to act on its own**.

  $\Rightarrow$ It needs a co-infector (**helper adenovirus**).

- AAV has **serotype** associated depending on the targeting region (in this study AAV8).

Obesity

- People with BMI ≥ 30,
- Affects more that a third of the American adults,
- Obesity and overweight were associated with almost 20% of the deaths in the US,
- Leads to complications such as: cardiovascular diseases, type 2 diabetes, stroke.

Type II diabetes, Kidney failure

- According to the WHO: more than **1.5 million deaths** directly associated with **diabetes**,
- Kidney(renal) failure widely spread in the US with **more than 600000 people annually** on dialysis or in need of a kidney transplant.

Heart failure

Heart failure – not solely represented by having a heart attack, but it is mostly represented by patients whose hearts can no longer pump at 100% capacity.

More than 400000 deaths annually directly associated with it.

Actual contribution

Article's structure

Composed of 4 disease models:

- The first one targets obesity
- The second one targets type II diabetes
- The third one targets kidney failure and renal fibrosis
- The fourth one targets heart failure

First disease model

- They've used **adult non-transgenic mice**,
- Some mice were fed a normal diet, while other were fed a high-fat diet 3 months before the experiment,
- HFD mice were infected with each individual AAV or in some combination.

First disease model

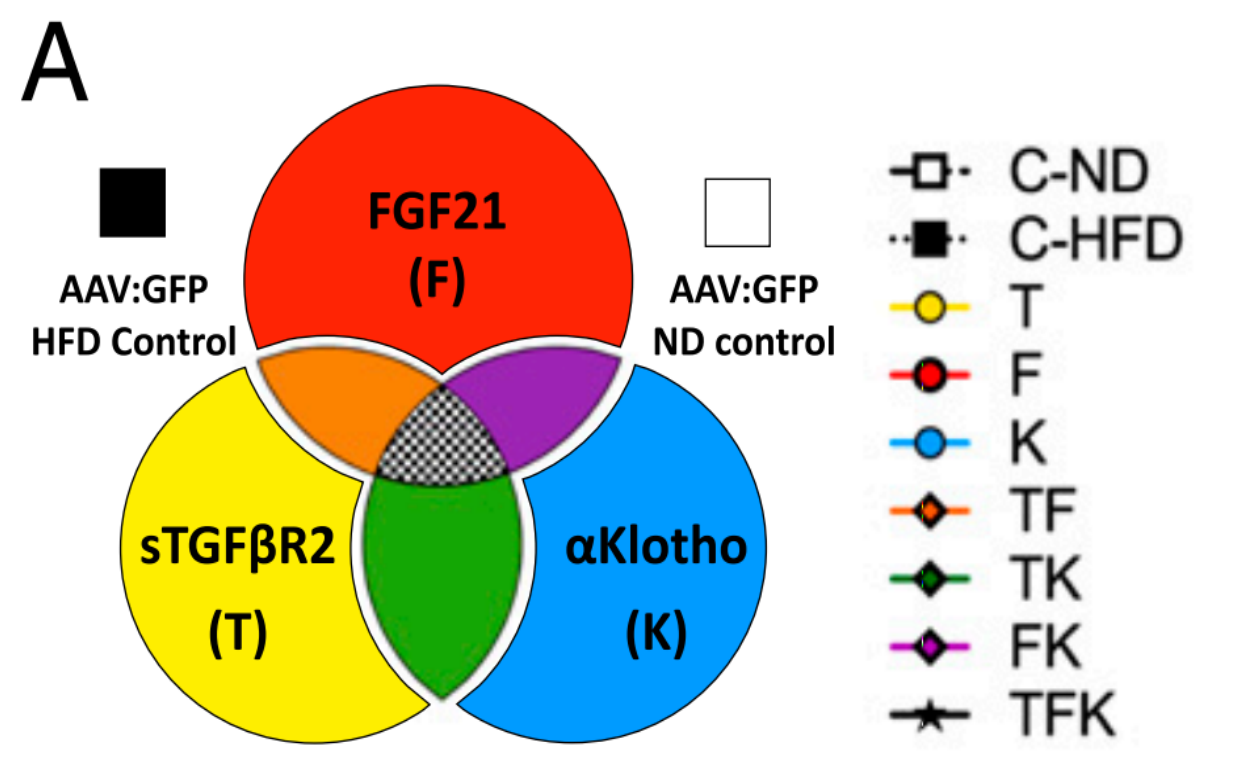

Figure 1: Venn diagram of the combinations of gene therapies explored as well as the color coding for all subsequent graphs.

First disease model

Results showed that:

- AAV:FGF21 recipients experienced a **complete reversal** of the obese phenotype within 40 days post injection,
- this phenotype **was maintained** throughout the study despite the continued HFD

First disease model

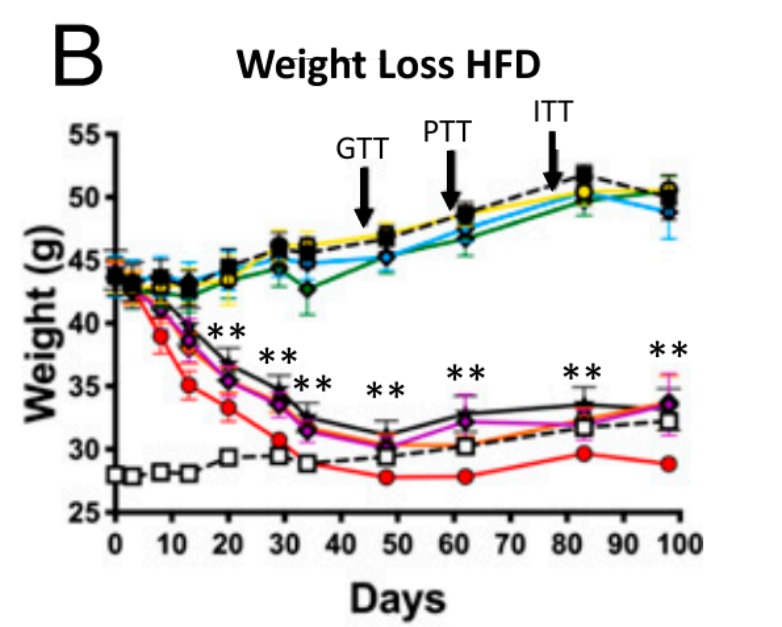

Figure 2: Weight of injected mice over time.

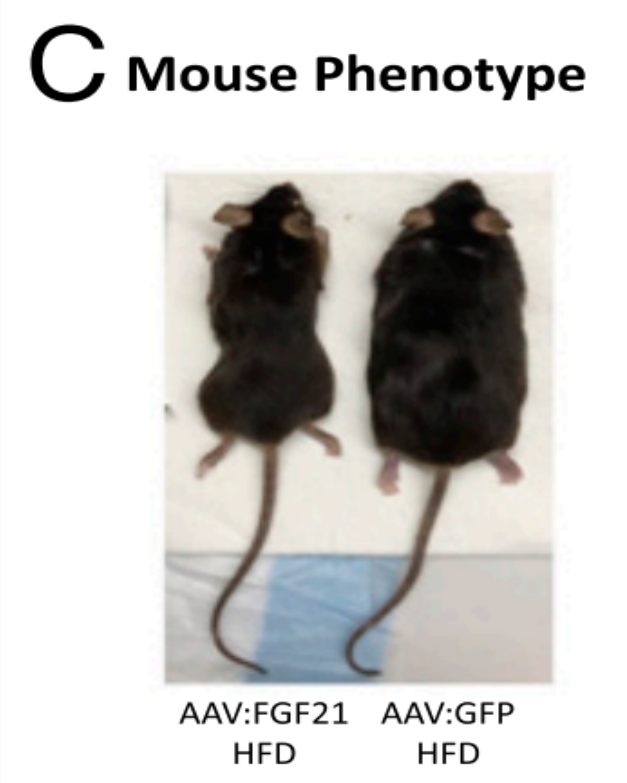

Figure 3: Phenotype exhibited by mice on an HFD control vs. injected.

First disease model

To evaluate if the same therapy could mitigate age-related obesity:

- there were used 18-months old mice,
- all of them on a normal diet (since these mice tend to naturally experience increased adiposity).

Results showed that:

- AAV:FGF21, but also AAV:αKlotho recipients experienced a **decrease in weight**,
- this decrease was maintained until at least the 150 days mark.

First disease model

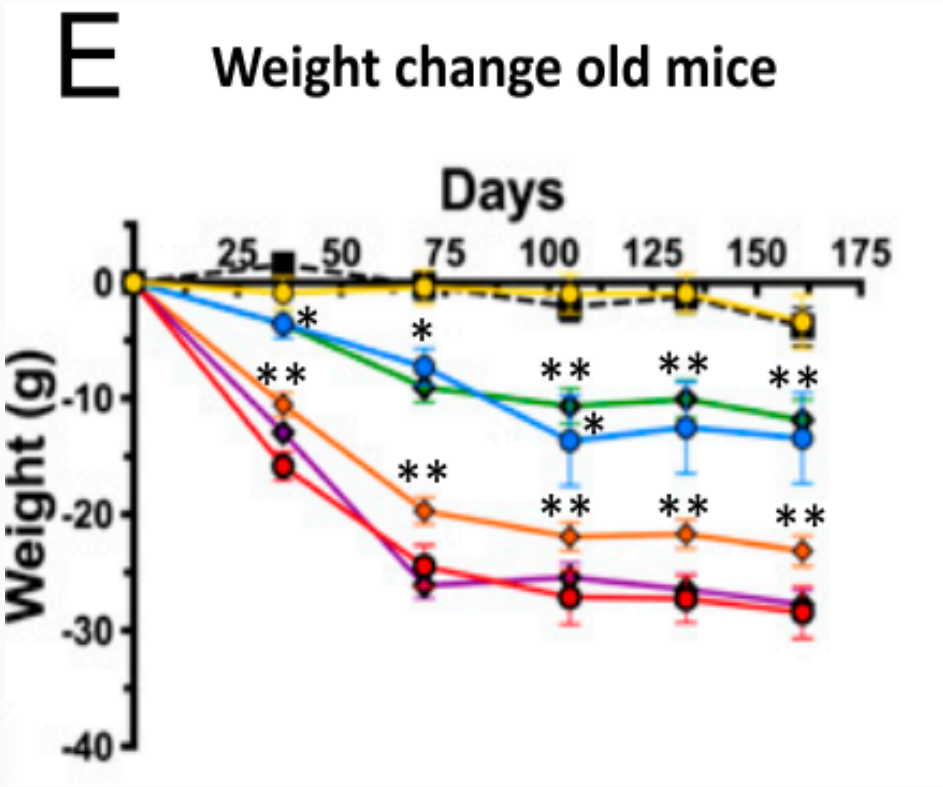

Figure 4: Percentage weight change of 18-mo-old mice on an ND with starting weight 40 g.

Extra tests – metabolic chamber

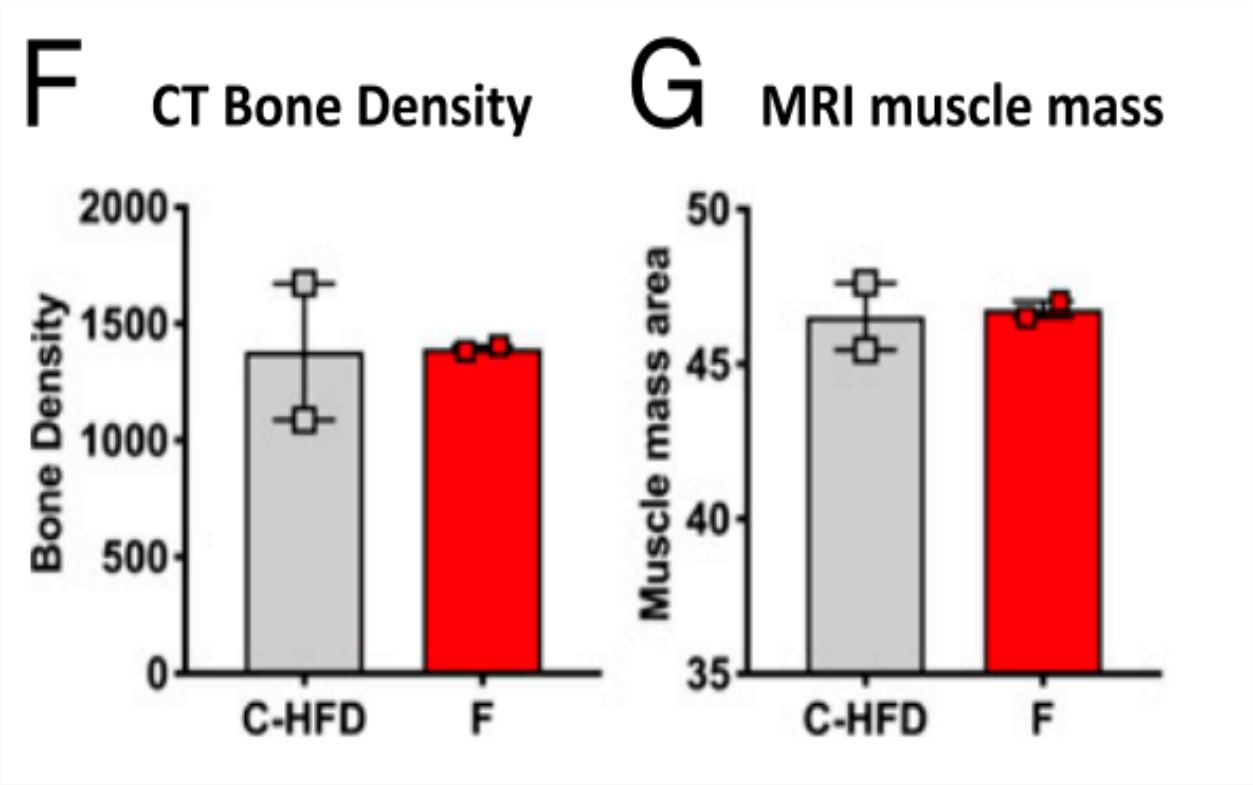

Figure 5: CT scan of mice observing bone density after administration of AAV:FGF21. Quantified muscle mass of MRI of whole mouse

Second disease model

The second disease model investigated the effect of these therapies using:

- a glucose tolerance test(GTT),
- an insulin tolerance test(ITT),
- a pyruvate tolerance test (PTT),
- fasting blood glucose measurements.

Second disease model

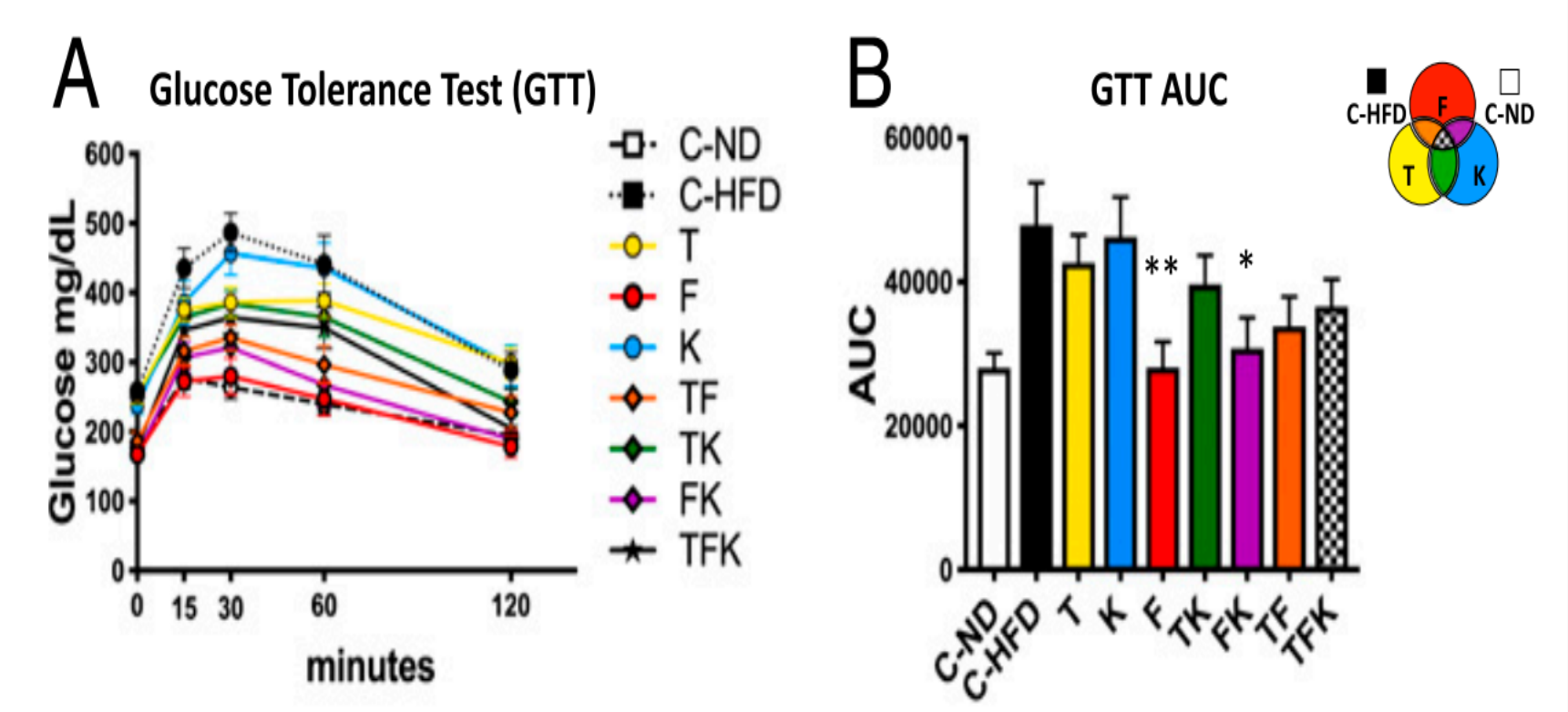

Figure 6: GTT of mice fasted overnight for 8 h. Blood glucose measured at 0, 15, 30, 60, and 120 min after oral gavage of 50 mg of glucose

Second disease model

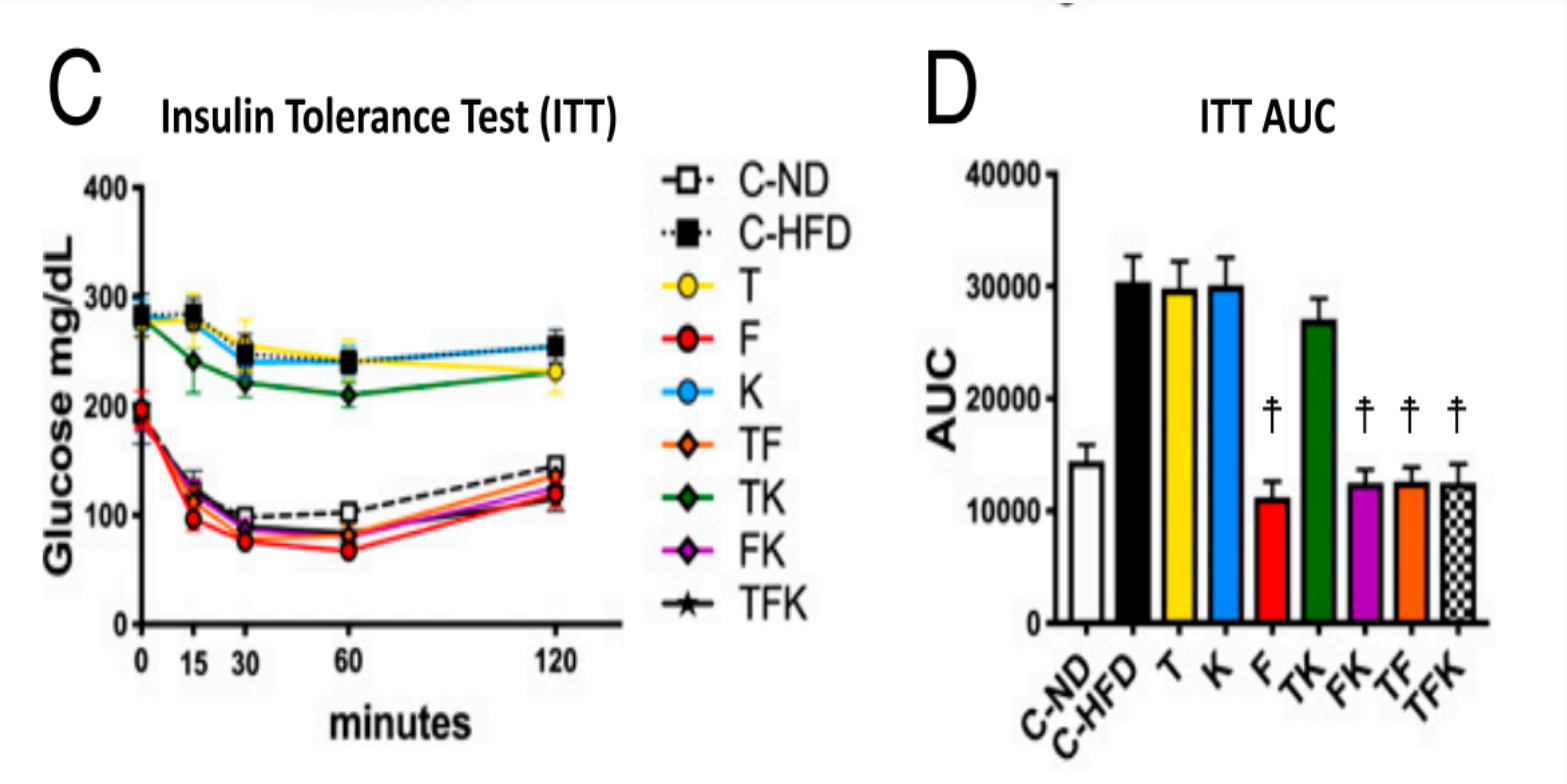

Figure 7: ITT of mice fasted for 6 h. Blood glucose measured at 0, 15, 30, 60, and 120 min after subcutaneous injection of 0.5 IU/kg insulin.

Third disease model

The third disease model used unilateral ureteral obstruction(UUO).

Mice were:

- injected with gene therapies 1 week prior to UUO induction,
- analyzed for fibrosis and remodeling 1 week after UUO.

Third disease model

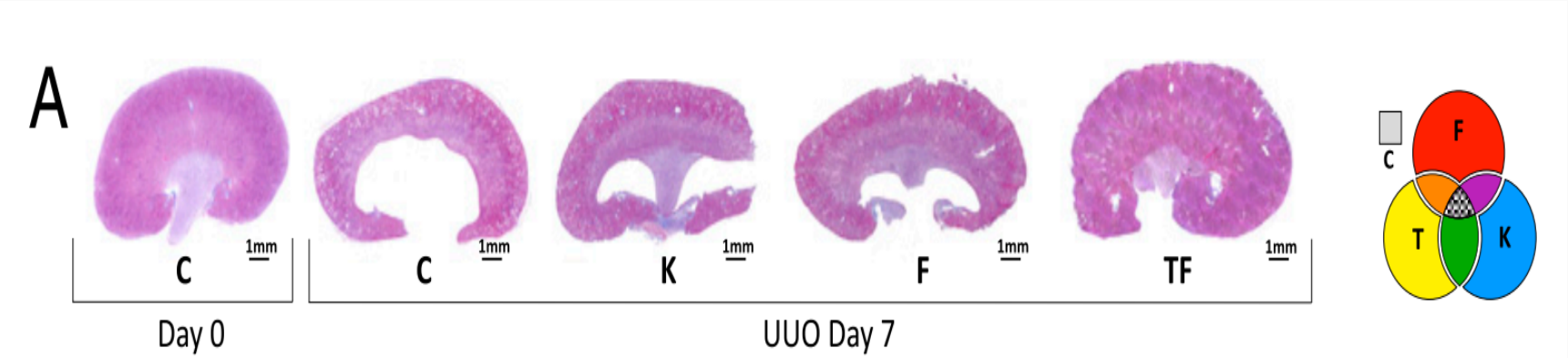

Figure 8: Overexpression of αKlotho and FGF21 were able to prevent deterioration of the renal medulla and thinning of the renal cortex compared with controls.

Fourth disease model

Ascending aortic constriction(AAC) was selected as the fourth disease model.

Six-month old mice were **injected with gene therapies 1 week prior** to ECHOSs and AAC surgeries.

- ECHOs didn't reveal any influence of these therapies on normal heart function,
- the surgical survival rates varied: 77% for AAV:sTGFbR2, 87% for AAV:sTGFbR2 + AAV:αKlotho vs. 50% for control mice.

Fourth disease model

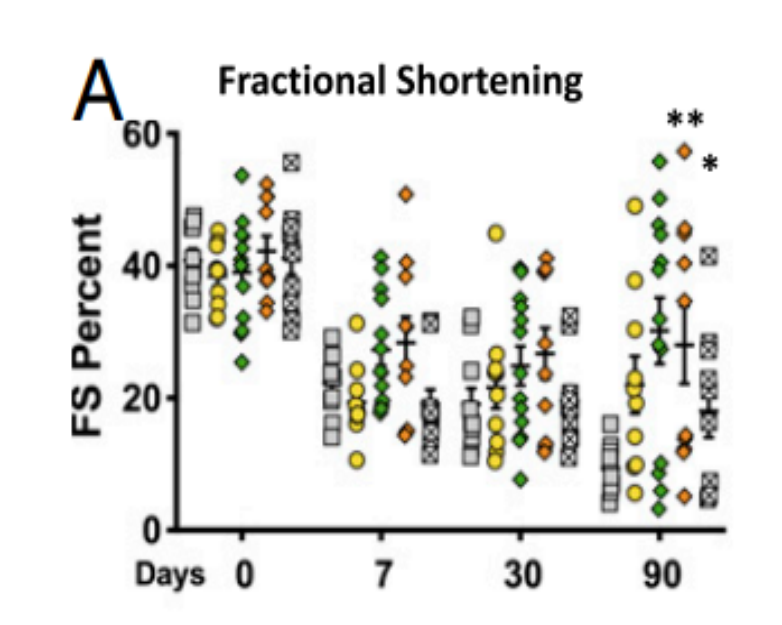

Figure 9: FS quantification of ECHOs at baseline and 7, 30, and 90 d postsurgery.

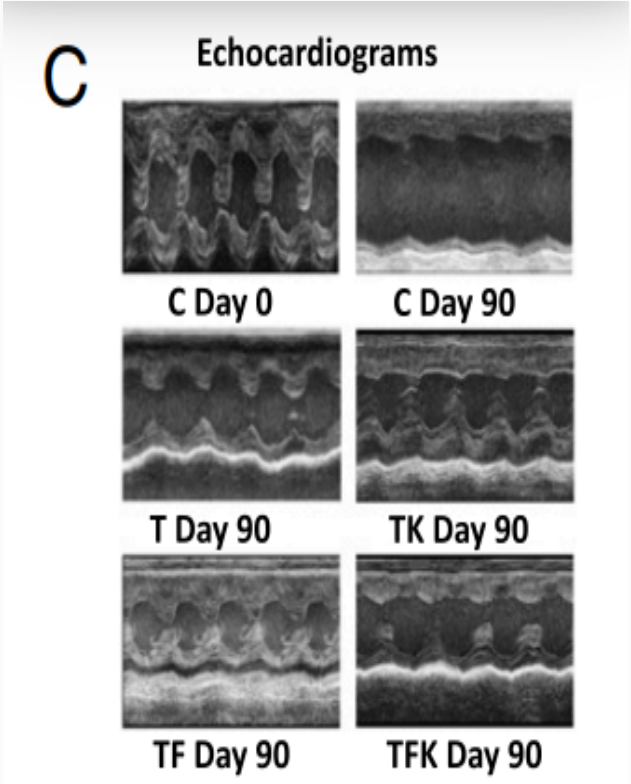

Figure 10: Quantification of EF from ECHO.

Fourth disease model

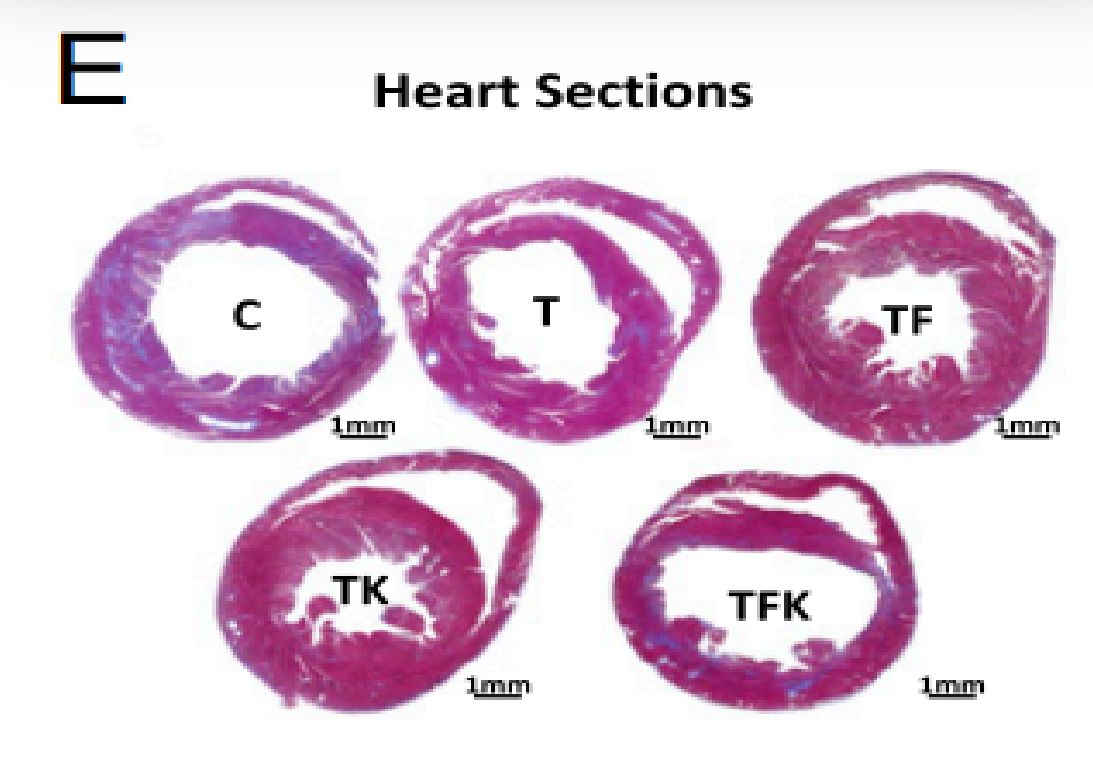

Figure 11: Representative image of MTS hearts taken at 10 and stitched together.

MTS sections revealed up to a 61% decrease in interstitial fibrosis.

Conclusion

Conclusion

After these 4 disease models, here are the best results:

- The obesity model: AAV:FGF21 either individually or in combination for both HFD middle-age mice and ND old-mice
- The type II diabetes model: all 3 therapies provided a substantial and lasting effect following a single administration and treated the HFD mice

Conclusion

- The UUO model: all therapies elicited a positive effect on medullary deterioration vs. control mice
- The AAC heart failure model: best results for the combinations of AAV:sTGFβR2 with either AAV:FGF21 or AAV:αKlotho.

$\Rightarrow$ **AAV:sTGFβR2 and AAV:FGF21 can successfully treat all 4 age-related diseases at once**

Questions?