

AMDCC

Purpose: To create an animal model of type II diabetes that also develops atherosclerosis

Summary of Animal Models Created Through Selective Breeding

1. Diet induced obese, hypercholesterolemic, insulin resistant, pigs that can develop diffuse atherosclerosis.
2. Nondiet induced hypercholesterolemic, insulin sensitive pigs that develop focal atherosclerosis.
3. Nondiet induced, hypercholesterolemic, downsized, insulin resistant pigs that develop diffuse atherosclerosis.

Characteristics of Diet Induced Obese Hypercholesterolemic, Insulin Resistant Pigs

1. Obese. Increased percent body fat. Major increases in weight are induced with diet.
2. Hypercholesterolemia. Significant increase in total cholesterol that is diet induced.
3. 3. Insulin resistance. Of 18 animals that have been intensively analyzed(multiple determinations) 16 have insulin resistance.
4. Diabetes. Of 18 animals that have been analyzed, 7 have developed type II diabetes and 4 have worsening glucose tolerance.
5. Atherosclerosis. The animals with severe insulin resistance can develop diffuse atherosclerosis in the coronary arteries.

Characteristics of FH Animals

1. Cholesterol values that are comparable to pigs with diet induced hyperlipidemia.
2. Leaner than the pigs with diet induced hyperlipidemia.
3. More insulin sensitive.
4. Do not develop worsening insulin resistance over time.
5. Coronary artery atherosclerosis is present that it is proximal, focal disease.

Changes in 12 Animals that Completed 3 Months

	Basal FG	3 mo FG	Basal FI	3 mo FI	Basal SI	3 mo SI
051	97 ± 1	96 ± 1	16.3 ± 2.1	15.9 ± 3.1	32.3 ± 4.9	47.6±4.4
06I	111 ± 4	126 ± 7	8.2 ± 0.8	15.2 ± 2.3	19.5 ± 4.1	41.9±8.7
05B	107±6	186±11	12.0±2.5	10.0±1.9	12.1±2.9	12.2±2.6
02C	100±2	133±4	6.1±0.9	16.1±2.4	12.7±2.2	18.2±4.3
30B	115±7	168±5	22.9±3.1	52.0±2.8	36.1±5	64.7±8.4
34G	77±1	95.0±2	7.3±0.7	12.5±1.2	33.9±3.4	64.7±8.4
33G	68±3	75±2	7.9±1.1	13.1±1.9	42.9±6.2	102.8±11.1
116	104±6	99±12	34.4±3.7	24.1±3.7	75.1±6.6	75.7±8.7
69G	101±2	64±6	7.2±1.4	5.8±0.8	19.3±4.2	15.9±3.9
69F	110±3	115±5	15.5±1.7	16.5±2.2	33.8±4.5	27.7±3.6
*06F	118±5	130±4	7.5±0.9	6.2±1.0	17.7±2.1	11.3±2.8
02F	103±3	67±1	10.1±1.2	7.8±0.6	36.5±3.9	15.2±2.9
Mean	101±9	113±12 (p<0.05)	11.3±3.4	16.8±5.1	23.6±7.4	38.7±10.9

Glucose and Insulin Values at Baseline in NL Animals

	Number Fasting Glucose	Fasting Insulin	Stimulated Insulin
02I	96±3.4	11.9±1.1	28.6±2.7
01F	104±4.9	11.2±1.3	22.4±1.6
68F	125±2.2	8.1±0.8	12.5±3.3
62F	111±0.6	6.6±0.8	13.9±2.8
35G	113±1	17.8±3.6	47.6±6.2
03I	117±7.1	7.3±0.9	25.4±3.9
Mean	111±4.3	10.5±2.0	25.1±8.6
Mean (n=12)	101±9	11.3±3.4	23.6±7.4

Glucose and Insulin Changes in 4 animals that Completed 12 Months

	Baseline	3 mo	6 mo	12 mo
		<u>Fasting Glucose</u>		
*69G	101±2	64 ±6	78 ±3	138 ±4
69F	110± 3	115 ± 5	126 ± 6	121 ±7
*06F	118±5	130±4	130 ±2	165 ±7
*02F	103 ± 3	67 ± 1	94 ± 4	144 ± 4
Mean (SD)	108 ± 4	94 ±21	108 ±9	142 ±17
		<u>Fasting Insulin</u>		
69G.	7.2±1.4	5.8±0.8	7.7±1.4	11.4±2.2
69F	15.5±1.7	16.5±2.2	29.3±2.1	18.0±2.1
06F	7.5 ±0.9	6.2±1.0	8.9 ± 2.2	19.9 ± 31
02F	10.1 ± 1.2	7.8 ± 0.6	6.4 ± 0.4	12.8 ± 0.5
Mean (SD)	10.0 ± 1.9	9.0±3.1	13.1±8.4	15.5 ±4.6
		<u>Stimulated Insulin</u>		
69G	19.3 ± 4.2	15.9 ± 3.9	26.2 ± 3.4	35.2 ± 3.7
69F	33.8 ± 4.5	27.7 ± 3.6	45.7 ± 3.0	39 ± 2.8
06F	17.7 ± 2.1	11.3 ± 2.8	18.2 ± 2.6	22.6 ± 3.1
02F	36.5 ± 3.9	15.2 ± 2.9	14.8 ± 1.7	17.5 ± 1.2
Mean (SD)	26.8 ± 6.2	17.5 ± 4.8	26.2 ± 5.6	28.5 ± 4.9

Changes in 6 FH Insulin Sensitive Animals after 12 Months

<u>Animal Number</u>	<u>Baseline</u>	<u>Fasting Glucose</u>		
		<u>3mo</u>	<u>6 mo</u>	<u>12 mo</u>
51F	104	72	56	71
52F	81	74	78	77
47F	79	75	79	66
49F	102	82	80	76
103G	90	74	94	90
106G	72	79	80	83
Mean	88 ± 6	76 ± 4	78 ± 10	77 ± 6
		<u>Fasting Insulin</u>		
51F	13.1	9.3	5.9	5.1
52F	9.9	7.0	8.8	6.3
47F	7.0	5.7	7.4	3.8
49F	8.9	7.5	7.0	8.7
103G	9.9	9.2	8.9	9.4
106F	6.8	8.0	6.6	11.1
Mean	9.3 ± 0.9	7.8 ± 1.4	7.4 ± 1.5	7.4 ± 1.6
		<u>Stimulated Insulin</u>		
51F	24.5	17.6	13.9	8.3
52F	20.8	25.4	28.6	15.2
47F	14.9	23	36.8	24.3
49F	12.9	16.5	17.6	26.8
103G	18.6	20.1	16.8	18.8
106G	18.3	22.1	16.7	26.3
Mean	18.3 ± 3.2	20.7 ± 2.9	21.7 ± 3.0	19.9 ± 2.6

Change in Si values with Diet

	Baseline	3 mo	6 mo	12 mo
69G	4.1	4.3	4.5	3.6
02F	4.0	4.4	4.2	3.0
69F	3.9	4.2	3.7	3.4
06F	4.2	3.8	3.8	3.0
Mean	4.1	4.2	4.1	3.3

Change in Si Values in FH Animals

	Baseline	3 months	6 months	12 months
51F	4.5	5.0	5.0	5.0
52F	5.0	5.0	5.0	4.8
47F	4.8	5.1	5.2	5.0
49F	5.0	5.4	5.5	5.2
103G	4.9	4.6	4.8	4.7
106G	5.0	5.2	5.2	5.0
Mean \pm SD	4.9 \pm 0.1	5.0 \pm 0.3	5.1 \pm 0.2	5.0 \pm 0.1

Changes in Weight and Cholesterol

	Baseline	3 months	6 months	12 months				
	cholesterol	weight	cholesterol	weight	cholesterol	weight	cholesterol	weight

Normal

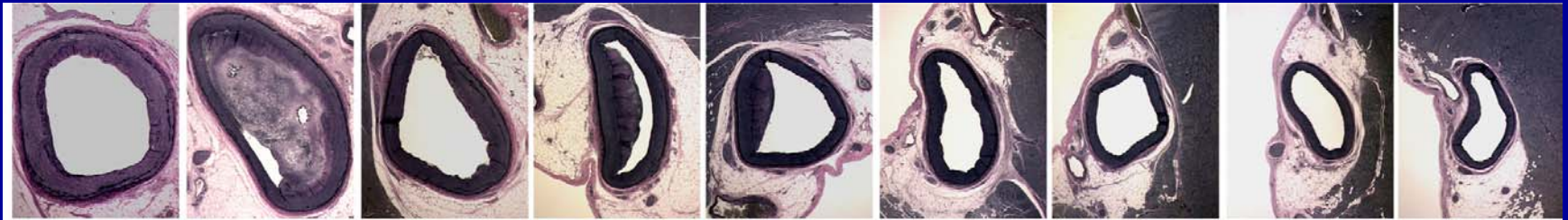
Lipid	Mean	67	429	494	418	451	459	338	555
	SD	18.5	42.0	262.6	34.4	256.1	45.7	66.2	19.7

FH	Mean	391	421	394	457	410	449	372	478
	SD	104.1	50.8	54.0	50.2	73.4	37.6	37.6	48.1

Extent of Coronary Atherosclerosis in NL/IR and FH/IS Pigs

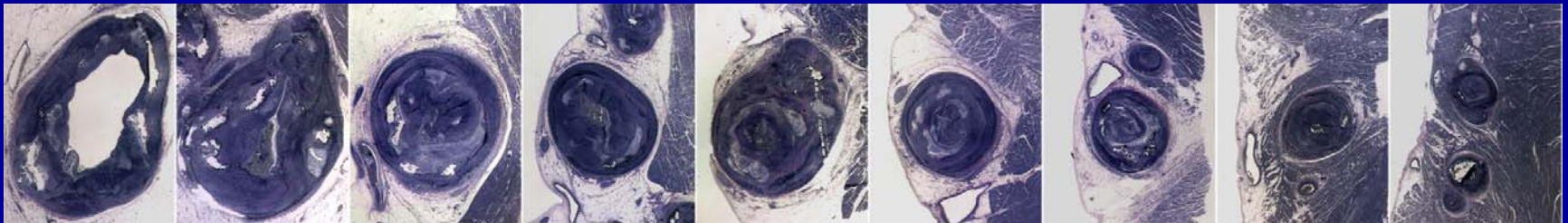
FH/IS LAD

% stenosis = 17.6 ± 5.8



NL/IR LAD

% stenosis = 86.9 ± 10.0



Atherosclerosis Morphometry

- Coronary Arteries
- Intimal/Medial Area
- FH/IS (n=5) .226 (.125)
- NL/IR (n=3) .726 (.321)

Conclusions

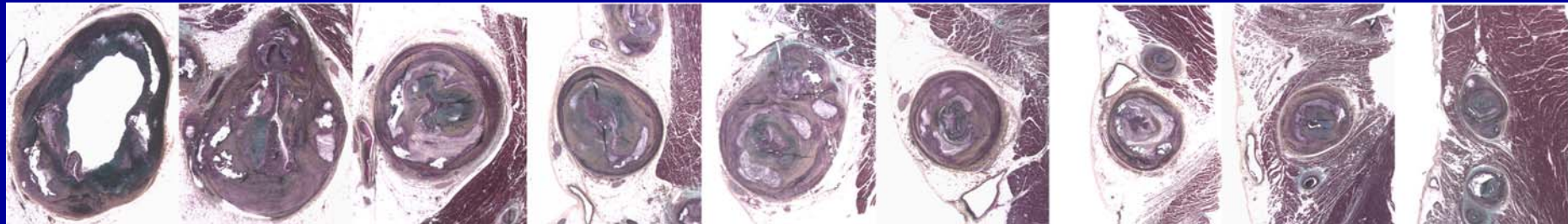
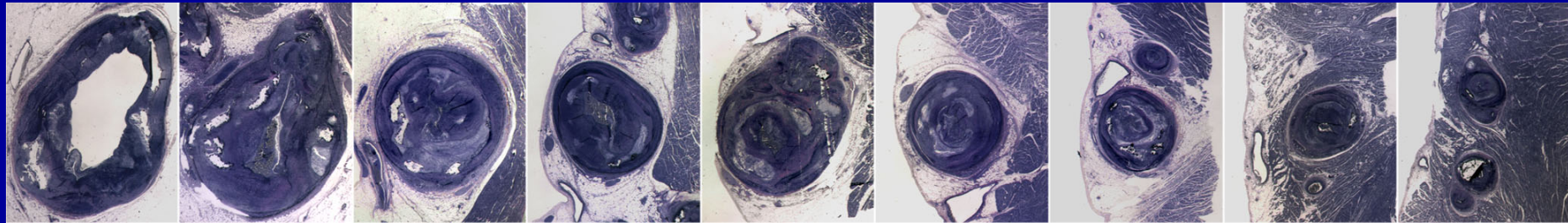
1. We have developed a model of diet induced insulin resistance.
2. Diet fed pigs develop progressively more severe insulin resistance.
3. A high percentage (e.g. 50%) of high fat diet fed pigs develop hyperglycemia.
4. The diet fed pigs that the been analyzed have developed more diffuse atherosclerosis compared to animals with a similar cholesterol who are insulin sensitive.
5. This model will allow us to determine if hyperglycemia is associated with a more severe atherosclerotic phenotype compared to insulin resistant normoglycemic animals.

Future Plans

1. Finish the 12 month analysis on pigs being fed a high fat diet.
2. Determine the efficacy of femoral ultrasound in predicting coronary, carotid and femoral artery disease progression.
3. Determine if the lipoprotein profile is different in diet induced hypercholesterolemic, insulin resistant pigs compared to insulin sensitive, FH animals.
4. Determine if hyperglycemia is associated with more diffuse and severe atherosclerosis compared to insulin resistance alone.
5. Selectively breed downsized FH animals in an attempt to create insulin resistant hypercholesterolemic animals and determine the severity of their atherosclerotic phenotype.

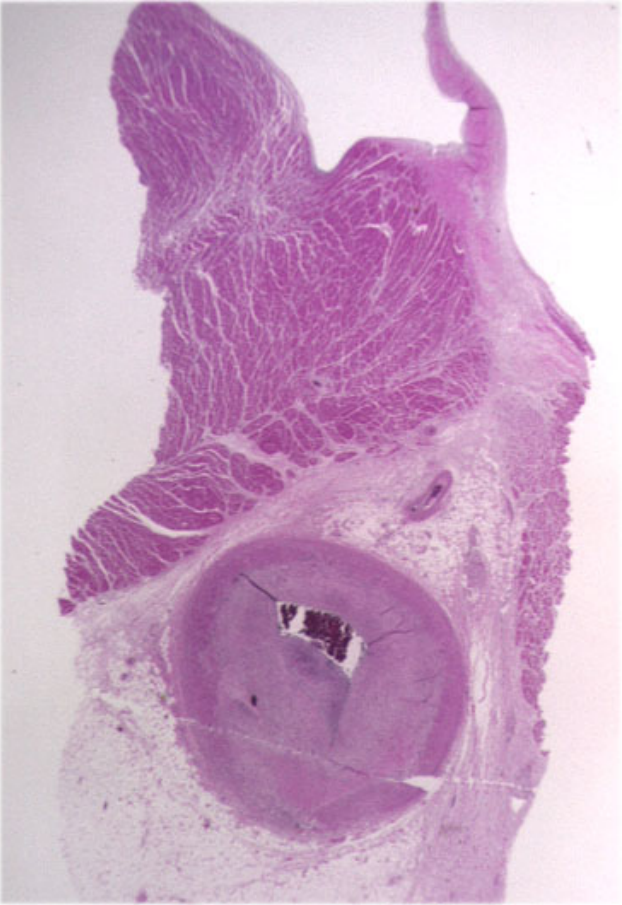
Coronary Atherosclerosis in IR pigs

Movats vs VVG

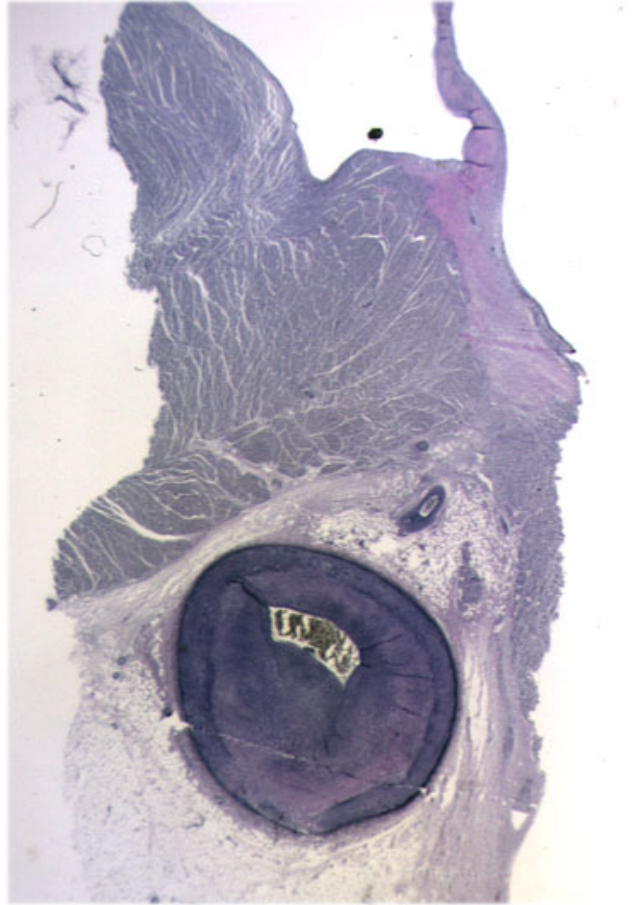


Coronary Atherosclerosis in IR pigs

H & E



VVG



Movats

