

Purpose/Mission

The Center on Diabetes, Obesity, and Metabolism (CDOM) supports investigators across the WFUSOM and Advocate Healthcare System whose research addresses metabolic disease and how metabolism affects all disease processes. The CDOM has a special role in supporting the aLHS in translating research into better patient care and using patient outcomes to inform research (forward and reverse translation).

Leadership and Membership

Led by Don McClain MD, PhD and Leah Solberg-Woods at WFUSOM, the CDOM is also part of the North Carolina Diabetes Research Center (NCDRC), an NIH-supported (P30) Center with sites at Duke, NCA&T, UNC-Chapel Hill, and WFSOM, charged with providing support for diabetes research, particularly Early Career Investigators or those new to diabetes Research.

CDOM and NCDRC have 112 and 293 members, respectively, who together hold \$70,000,000 (annual direct \$) in federal research funding. Their research spans the full translational spectrum from basic and molecular to clinical, population, and implementation studies.

Training Components

CDOM and NCDRC investigators train medical, graduate, and postdoctoral trainees. The programs support \$400,000 annually in Pilot and Feasibility funds, largely targeted to Early Career Investigators.

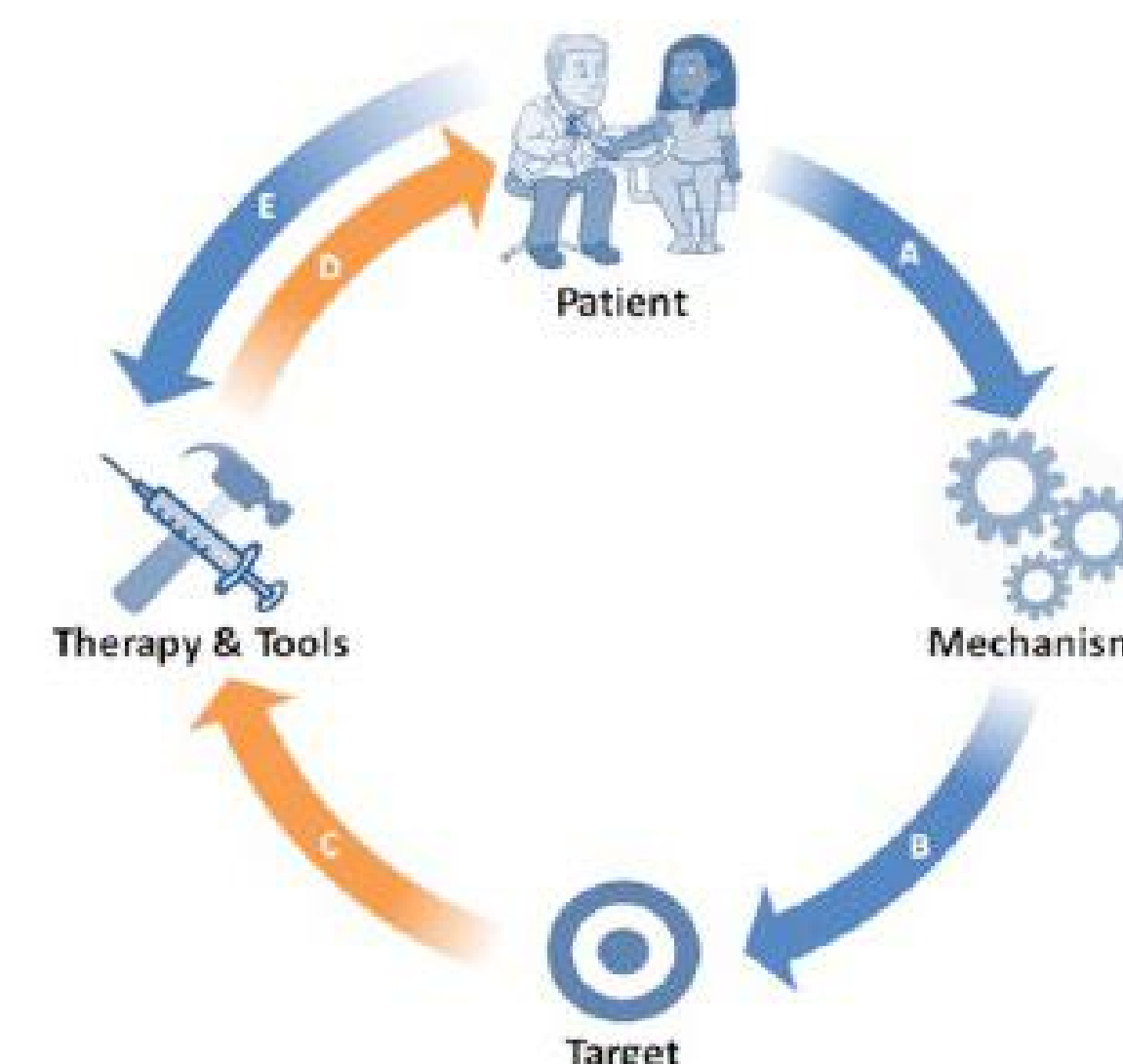
Areas of Research Expertise Include:

- Childhood and adult obesity clinical trials, including family interventions;
- Genetic underpinnings of diabetes and obesity;
- Diabetes management strategies in underserved populations;
- Using the latest technologies in diabetes research and disease management;
- Predictors of diabetic complications;
- Novel risk factors for diabetes (e.g., radiation exposure, micronutrients);
- Role of fat tissue in diabetes;
- Regeneration of insulin-secreting cells.

Research Project Spotlight

How does metformin work?

Translational research. A key function of the Learning Healthcare System (LHS) is *translation* of knowledge into better, safer clinical care (steps A-D, below). The academic LHS has an additional capacity, namely, to take patient data and outcomes back to the laboratory to expand knowledge of disease processes and pathways (*reverse translation*, arrow E). This process, in turn, can be reiterated by further translation into clinical care.



Example: How does metformin work?

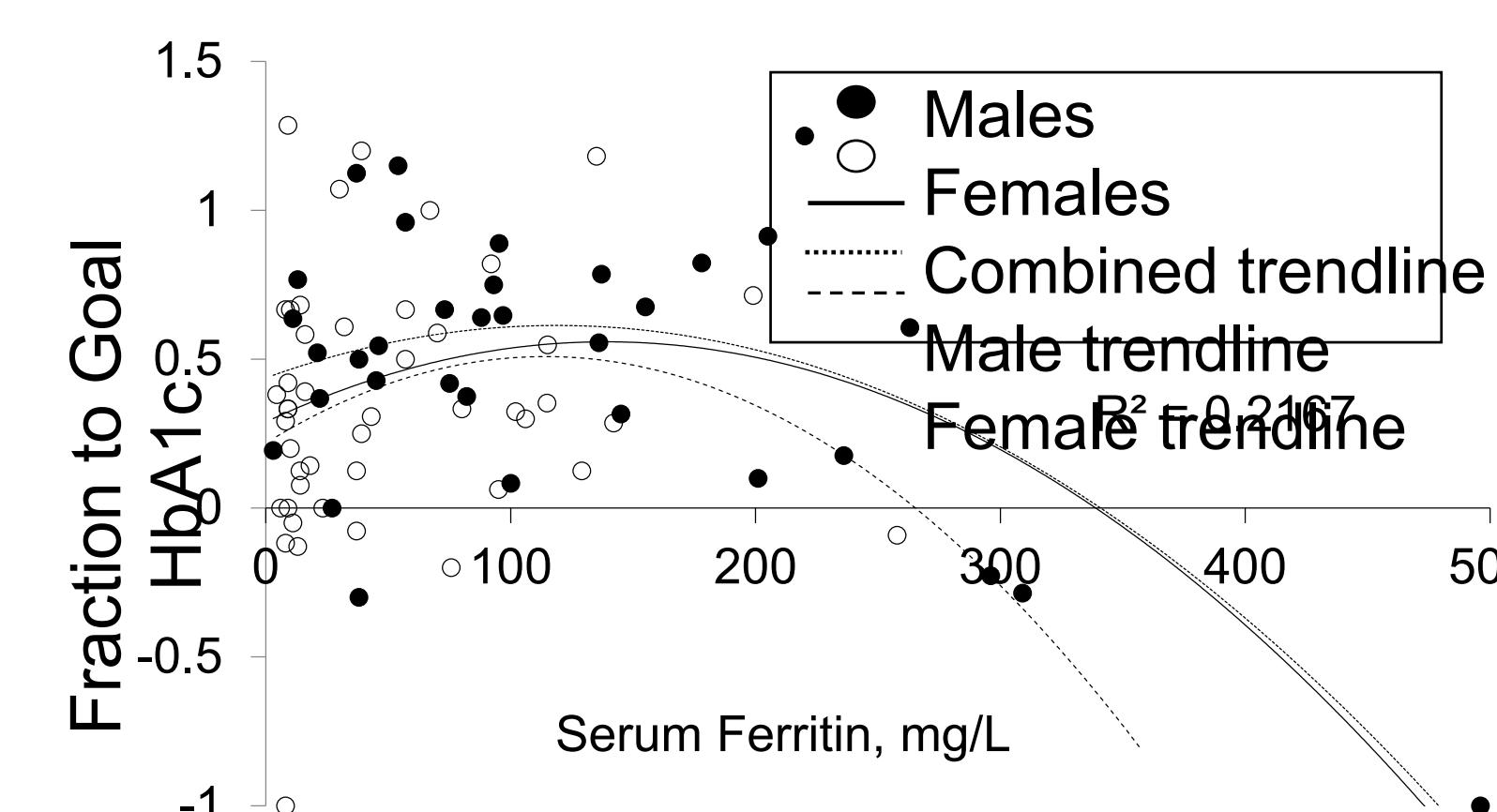
The drug metformin is the most widely prescribed drug for type 2 diabetes mellitus (T2DM) in the world and is being tested for possible benefits in Alzheimer's disease, aging, and certain cancers. Despite over 50 years of use, however, we still do not understand how it works! This knowledge could obviously point to new pathways to target for better treatment.

Iron and diabetes risk. High levels of dietary and tissue iron, even across the "normal" range, are a risk factor for T2DM. Based on this work, we have an NIH-sponsored clinical trial to see if reducing iron by blood donation improves T2DM.

Do iron levels affect the metformin response?

An experiment done in yeast showed metformin initiated a so-called "iron starvation response." If this were so in humans, we reasoned that people already low in iron would have already triggered that response and might not get much further help from metformin. At the same time, very high iron might overwhelm the system and prevent a good metformin response.

To test this hypothesis, we used the resources of our Clinical and Translational Science Institute, supported by the NIH CTSA consortium, to look at how iron affected the response to metformin in terms of improving hemoglobin A1c, the main clinical indicator of diabetes control.



Tissue iron, measured as serum ferritin levels, had the predicted effect: Both women and men with either low or high iron did not lower their A1c levels as well as those with mid-range iron.

Can we model this in a laboratory animal to facilitate further study? Studies of disease and drug mechanisms are often made easier in animal models, where studies can often be done more rapidly, cheaply, and in a more controlled fashion. We, therefore, fed mice a "fast-food" diet containing different levels of iron to achieve levels analogous to vegans, mid-normal, and heavy red-meat eaters.



Mice on normal iron (middle) developed diabetes and increased their blood glucose on the "fast food" diet, and that was prevented by metformin. On low iron, the mice behaved like they were already on metformin and glucose did not increase, nor did metformin have any further effect. On high iron, glucose increased the most, and metformin was ineffective. The pathways controlling these responses are under study.

Conclusions:

Reverse translation is a powerful tool of the aLHS to translate research findings into more effective care. Academic collaborations benefit healthcare systems!

Too much iron, such as can occur with consumption of large amounts of red meat, as well as too little, is bad for you. Up to 80% of metformin "failures" can be attributed to too low or too high iron.

- Should the "normal" range of iron be amended to include an "optimal" range?
- The pathways that regulate these responses are potential targets for diabetes therapy.