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Diabetes pipeline-Clinical research in progress

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Prof. Lesley Campbell, professor of medicine, director of diabetes services, at Garvan Institute of Medical Research, Australia, is keen on clinical research and her focus has been in the cause of type 2 diabetes, particularly what triggers the insulin resistance and obesity that occurs in

To study the cause without the confounding influence of hyperglycaemia or dyslipidaemia, she studies healthy close relatives of people with type 2 etic influence.

So far her institute has published that such people—with a high probability of developing diabetes later in life—show deficiency in a satiety hormone response called Peptide YY (PYY)—while they are still weight in later life.

“We also see that they have a defect in turning on fat oxidation in response to a fat meal, which may cause the later metabolic abnormalities,” says Prof. Campbell. “Our work shows that the people who are to get diabetes already have a biological predisposition to weight gain (not just ‘willful overeating’ as is so often said) and in blood and tissue samples we are now able to isolate the mechanisms for the earliest changes contributing to the insulin resistance that characterizes the primary defect of type 2 diabetes (as opposed to type 1 diabetes).”

Another area of research for Garvan Institute has been to examine the challenge of the ‘orphan’ disease Prader-Willi Syndrome (PWS): the most commonly known genetic obesity disorder arise due to an imprinting defect on chromosome 15. A project to examine the intense, uncontrolled hunger that disrupts the life of the family and the sufferer of this developmental

disorder, sometimes resulting in PWS sufferers needing to live in care situations to restrain their eating.

“We have examined the satiety and hunger hormones of volunteer subjects from the Royal Prince Alfred PWS clinic in a very strongly matched way with obese subjects without PWS to tease out any real differences intrinsic to PWS. We have found higher immune activation that may be an intrinsic part of the disease,” says Prof. Campbell.

“We have completed a single dose pilot study of a novel therapeutic agent that is already released for diabetes and may bea potential treatment for PWS against appetite, as no medication is recognized as effective at present. This indicates the need for a longer trial. We are also examining the contributors to the increased cardiovascular risk in PWS subjects and are comparing the risk factors with matched obese and lean volunteers. In collaboration with Prof Herbert Herzog, also from the Garvan Institute, we have commenced a study by producing a mouse model of the disorder—the technology for which came recently—that allows the study of the brain with knockout of the gene and study of the phenotype,” she adds.

Garvan has submitted an intravascular ultrasound (IVUS) study of rosiglitazone post-stenting examining one year results in the coronary arteries of diabetic subjects having stents in another artery. Rosiglitazone has shown improved glycaemic control, lessened inflammation including adiponectin.

Dr Reddy’s Pharma, one of India’s top pharmaceutical companies by revenues and sales, announced successful phase III results of its balaglitazone in January 2010. Dr Reddy’s said preclinical studies indicated that besides robust glucose lowering ability, balaglitazone results in lower body fluid accumulation, lower fat accumulation, less heart enlargement and no reduction of bone formation, indicating that balaglitazone may be able to displace the balance between desired and side effects, and thus show a better safety profile than full agonists of PPAR-gamma.

Danish diabetes giant, Novo Nordisk, has two new-generation insulin products, Degludec and DegludecPlus—that are intended improve treatment outcomes and provide more convenient insulin therapy with a possibility of fewer injections. Currently in phase III development, the Degludec and DegludecPlus development programs will involve more than 10,000 patients from 39 countries around the world.

The trial program for Degludec is known as BEGIN and will involve more than 7,000 patients. Degludec has so far demonstrated an ultra-long duration of action of more than 24 hours, offering the potential of greater dosing flexibility and lower risk of hypoglycaemia. The trial program for DegludecPlus is called BOOST and will recruit over 3,000 patients. DegludecPlus is the first soluble combination of an ultra-long-acting basal insulin with a boost of rapid-acting insulin (NovoRapid).

Novo Nordisk is also focusing on the development of oral protein formulations for both insulin and GLP-1 for the treatment of diabetes. Since data from Drug Abuse Warning Network (DAWN) database and elsewhere show that injections continue to be a barrier to insulin initiation among physicians treating diabetes, Novo Nordisk believes that the introduction of a safe and effective oral insulin (and GLP-1) product to the market could lead to earlier use of insulin in diabetes treatment, and hence, the potential for better treatment outcomes and reduced risk of disease-related complications in people with diabetes all over the world.

In an interview with BioSpectrum, Jesper Hoiland, senior vice president of international operations, Novo Nordisk, says a oral insulin pill was introduced in Germany in December 2009 and is in a phase I clinical trial. “In the long run, within eight to 10 years we can see the diabetes pill becoming available in the markets.” According to him the oral insulin looks fine in clinical trials done so far.

The power of prevention

Prof. Campbell of Garvan Institute says no prevention trial of type 1 diabetes is known to be successful. Insulin therapy in type 1 diabetes has been improved by insulin analogues, usually treated with background dept insulin and short-acting analogue with each meal, but young people in particular are using insulin pump therapy. Continuous glucose monitoring is not commonly used. Transplants are offered only to those with complications such as renal failure or severe hypoglycemia.

For many people, type 2 diabetes can be managed or prevented by a healthy diet and regular exercise. Many people worldwide do not know they have diabetes, and many of those who do know are in poor control of their diabetes. Lifestyle change is still the first option for the treatment of type 2 diabetes, experts say that treating diabetes at an early stage improves quality of life, but is cost-effective, especially if it prevents hospitalization. There is conclusive evidence that good control of blood glucose levels can substantially reduce the risk of developing complications in all types of diabetes.

Financial burden

Diabetes imposes a large economic burden on the individual, national healthcare system and economy. Healthcare expenditures on diabetes are expected to account for 11.6 percent of the total healthcare expenditure in the world in 2010.

Most countries will spend between five and 13 percent of their total healthcare dollars on diabetes.

According to IDF Diabetes Atlas, estimated global healthcare expenditures to treat and prevent diabetes and its complications are expected to total at least Rs 16,71 lakh crore ($376 bn) in 2010. By 2030, this number is projected to exceed Rs 21.77 lakh crore ($490 bn). Expressed in International Dollars (ID), which corrects for differences in purchasing power, estimated global expenditures on diabetes will be at least ID418 bn in 2010, and at least ID561 bn in 2030. An estimated average of $703 (ID878) per person will be spent on diabetes in 2010 globally.

There exist a large disparity in healthcare spending on diabetes between regions and countries. More than 80 percent of the estimated global expenditures on diabetes are made in the world's economically richest countries, not in the low- and middle-income countries where over 70 percent of people suffer from diabetes.
The US, is projected to spend Rs 8.80 lakh crore ($198 bn) or 52.7 percent of global expenditure in 2010, while India, the country with the second largest population of people living with diabetes, is expected to spend an estimated Rs 12,444 crore ($2.8 bn), or less than one percent of the global total. An estimated average of Rs 3.28 lakh ($7,383) per person with diabetes is expected to be spent on diabetes-related care in the US but less than Rs 444 ($10) per person will be spent in Burundi, Côte d'Ivoire and Myanmar in 2010.

The World Health Organization (WHO) predicted net losses in national income from diabetes and cardiovascular disease of ID557.7 bn in China, ID303.2 bn in the Russian Federation, ID236.6 bn in India, ID49.2 bn in Brazil and ID2.5 bn in Tanzania (2005 ID), between 2005 and 2015.

The largest economic burden, therefore, is the monetary value associated with disability and loss of life as a result of the disease itself and its related complications. This economic burden, however, can be reduced by implementing many inexpensive, easy-to-use interventions, most of which are cost-effective or cost-saving, even in the poorest countries.

Unraveling type 1 diabetes
Type 1 diabetes is increasing three percent per annum globally, according to Eurodiab and WHO registry. Several factors are thought to play a part (including increasing recognition of slow onset, non-classical type 1 diabetes in children and LADA, late onset type 1 diabetes) in older adults. The possible environmental factors include infectious exposure, vitamin D deficiency, less exercise and more obesity.

Scientists at The Scripps Research Institute in the US recently unraveled the 40 year old mystery of how certain genetic mutations lead to type 1 diabetes. The researchers says their findings could lead to novel therapies for type 1 diabetes and other autoimmune diseases. Three genetic variations in particular (HLA-DQ2, HLA-DQ8, and HLA-DR0405)-all located in the region of the genome called human leukocyte antigen (HLA) are known to increase risk of diabetes.

These three genes encode molecules that present peptides to the body's T cells, which determine whether the peptide being presented is dangerous and needs to be eliminated from the body, as in the case of foreign invaders such as bacteria or viruses-or whether the peptide is 'self', part of the host and something the immune system needs to leave alone. However, in the context of type 1 diabetes, T cells aggressively attack the body's own cells. While type 2 is responsible for most of the increase in diabetes.

HEALTH EXPENDITURE FOR DIABETES IN 2010-APAC

Country/Territory	2010 Population (20-79 years) (000's)	Mean health expenditure(US$) per person with diabetes
Australia	15127.7	3781
China	964301.6	115
China, Hong Kong	5732.5	N/A
China, Macau	382.9	N/A
Indonesia	152827.7	41
Japan	96665.9	3125
South Korea	36602.9	1255
Malaysia	16919.9	325
New Zealand	2952.4	2965
Singapore	3433.2	1129
Taiwan	14221.6	N/A
Thailand	45924.4	144

India	713498.4	55
Philippines	50999.8	61

DIABETES RESEARCH PIPELINE

BIOCON

IN -105 (Oral Insulin)

Subcutaneous insulin is very effective in the treatment of diabetes but its prescription is generally delayed due to inconvenience of needle usage and potential hypoglycemia (caused by excess insulinization). In contrast, Oral insulin (ie. Insulin in tablet form) is simple and painless to administer. Additionally, it is delivered through the portal vein, mimicking the natural physiology of the body. If successful in the clinic, oral insulin could become a very important therapy for intervention in earlier stages of diabetes.

Biocon is developing IN -105, a conjugated insulin molecule that is orally delivered and targeted towards the treatment of diabetes. In 2009, the company has made significant progress along its development life cycle. Biocon's R&D group has successfully developed a tablet for oral delivery of IN -105, its formulation carefully selected to give consistent absorption and glucodynamic (glucose-lowering) effect. In the clinic, this molecule has completed phase I and initial dose-range-finding phase II trials.

TAKEDA

Insulin pipeline

SYR-322 is a promising pipeline drug for the treatment of diabetes, following Takeda's core product Actos. SYR-322, which acts as a DPP-4 inhibitor, was discovered by Takeda San Diego (TSD) as a therapeutic agent for type 2 diabetes. Takeda is also working to develop a product combining SYR-322 with Actos.
Short-acting insulin secretagogue diabetes concomitant therapy with thiazolidinediones.

- Insulin sensitizer
  - Diabetes Concomitant therapy with thiazolidinediones
  - Diabetes Concomitant therapy with insulin
  - Diabetes Concomitant therapy with biguanides
  - Diabetes Fixed dose combination with extended-release metformin
  - Diabetes Fixed dose combination with metformin
  - Diabetes Fixed dose combination with glimepiride
  - Diabetes Orally disintegrating tablet
- Alpha-glucosidase inhibitor
  - Prevention of the onset of type 2 diabetes with impaired glucose tolerance (IGT) DPP-4 inhibitor
- DPP-4 inhibitor
  - Diabetes
  - Diabetes Fixed dose combination with Actos
  - Diabetes Concomitant therapy with thiazolidinediones
  - Diabetes Fixed dose combination with metformin
- Neurotrophic factor production accelerator
  - Diabetic neuropathy
- Glucose-dependent insulin secretagogue

Sanjeev Jain in Bangalore