What amphibians and fish can teach us about the brain

Vance Trudeau studies the effects of pollution on brain function and their implications for environmental and human health

by Tony Martins

What secrets might a healthier frog population help reveal about the human brain? **Vance Trudeau** and his colleagues are opening a door to the answer.

Known internationally for his groundbreaking work in the neurobiology of fish and frogs—and most recently for his "love potion" that led to frogs reproducing in captivity for the first time—the associate professor of biology at the University of Ottawa is determined to help clarify the connections between healthy environments and healthier brains.

"The part of the brain we study is very similarly organized in fish, frogs and mammals," explains Trudeau. "The hormones that control reproduction in fish and frogs are virtually identical in humans."

This striking likeness offers a scientific pathway toward healthier amphibians and humans.

"We want to help industries remediate effluents so that environmental impacts can be lessened or eliminated," notes Trudeau, "so we first have to find out potential effects in sensitive test organisms like frogs."

"Bad news," such as the recent B.C. Supreme Court findings on the complex causes of the drastic decline of sockeye salmon in the Fraser River, is a motivator for such research, says Trudeau, partly because of discordant opinions on what defines environmental health.

"Many understand that a clean environment means good health for animals and humans," he says. "Others are still in denial and are stuck in the 19th- or early 20th-century mode of thinking, that is to say that water is limitless and can handle the pollution loads. The latter is clearly not true."

Indeed, the evidence is overwhelming, including global declines in frog and other amphibian populations observed since the 1980s. These critical threats to global biodiversity remain poorly understood but Trudeau and his colleagues took a key counteractive step last year when they developed a "love potion"—a synthetic hormone mixture—to breed leopard frogs in captivity.

"The whole concept has changed my focus to helping zoos, researchers and conservation groups and encouraging them to start captive breeding," says the biologist. "There is a global amphibian decline and we need to do something drastic to help."

The breakthrough has since expanded and Trudeau now uses the method on other amphibian species, including salamanders.

"I am optimistic that we can assist anyone who wants to breed frogs for reintroductions," he says. "The problem is always whether the animals we place back in nature have a clean habitat that won't be ploughed under."

Leveraging the amphibian-human neurological link, Trudeau and international collaborators are using frog models to study several issues affecting humans, including the role of estrogens in embryonic development, the impact of petroleum mining chemicals on hormone release, and how agricultural pesticides affect sexual development.

Some of Trudeau's research involving fish, meanwhile, is helping to establish the role of a brain peptide called secretoneurin that he and his colleague Ajoy Basak think is a new vertebrate reproductive

"Applying the principles of comparative biology and evolution can provide ideas and solutions for human health problems. This requires important collaborative efforts between folks like me in biology and other researchers in medicine."
– Vance Trudeau

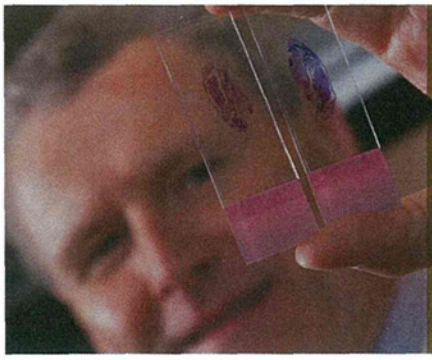
hormone. In a separate study, they are exploring the development of glial cells and neurons in fish because "fish have a great capacity for regeneration of cells in the brain," Trudeau notes. "If we can understand why fish can regenerate brain cells after neurotoxic insult, we may discover why mammals are so poor at doing this."

Although Trudeau's work is indirectly linked to the human brain, he and his collaborators are keen to contribute to the University of Ottawa's Brain and Mind Research Institute by drawing attention to the environmental factors affecting a healthy brain.

"The concept we have been developing based on our work with the brain is something called neuroendocrine disruption," says Trudeau. "Discussions over the years with graduate students led us to the conclusion that pollutants upset key hormones that the brain produces—hormones that control sexual behaviour, reproduction and feeding in both vertebrates and invertebrates."

"Applying the principles of comparative biology and evolution can provide ideas and solutions for human health problems," he adds. "This requires important collaborative efforts between folks like me in biology and other researchers in medicine." RP

THE QUEST FOR THE HOLY GRAIL



Michael Schlossmacher and his team investigate the relationship between a gene, a protein and approved drugs in the hope of finding a cure for Parkinson's

by Laura Eggertson

To design a new drug, test it through clinical trials and get it on the market costs millions of dollars and can take a decade or more. But if **Michael Schlossmacher** and his team are right, a drug that is already approved might save time, money and, most importantly, bring relief to people with Parkinson's disease.

Schlossmacher, a University of Ottawa neurologist who holds the Canada Research Chair in Parkinson's Disease and Translational Neuroscience, was recently awarded the Bhargava Research Chair in Neurodegeneration at the Ottawa Hospital Research Institute. He is studying the link between a gene called GBA1, a protein called alpha-synuclein and rapamycin, a drug that helps prevent rejection of transplanted organs.

Researchers have already demonstrated that most people with typical Parkinson's disease have greater levels of alpha-synuclein accumulated in their brain cells than people without Parkinson's. The protein clumps together in neurons, killing brain cells that produce dopamine, a chemical that enables neurons to communicate with each other. Loss of this chemical messenger contributes to the motor symptoms, such as stiffness, slowness and tremors, that Parkinson's patients typically experience.

People with two mutated copies of GBA1 in each cell develop Gaucher disease, a rare genetic disorder that causes problems in the liver, spleen, bone marrow and sometimes in the nervous system. People with Gaucher disease or with one mutated copy of GBA1 are at a higher risk for Parkinson's.

Recent genetic studies suggest that more than 10 percent of all people with typical Parkinson's may carry one mutated copy of GBA1, identifying it as the most common genetic risk factor and a potential treatment target for Parkinson's.

Schlossmacher discovered in 2011 that the normal form of GBA1 may play a protective role in the disorder. Working with Genzyme Corporation of Cambridge, Mass., Schlossmacher and his colleagues established that extra amounts of the enzyme the GBA1 gene produces can reduce the amount of alpha-synuclein in the brain cells of mice with Parkinson's-like behavioural changes. In these mice, extra amounts of GBA1 injected into the brain not only clear clumps of alpha-synuclein in affected brain cells, they also improve the rodents' performance on memory tests.

Academia-based laboratories, pharmaceutical companies, private foundations and federal funding bodies in the United States are exploring whether the GBA1-alpha synuclein link could be used to stem the process of neurodegeneration in people with Parkinson's disease. Genzyme sells an intravenous drug for enzyme replacement therapy to treat Gaucher disease. Now Schlossmacher wants to find out whether other drugs could also halt the process that causes alpha-synuclein to clump and kill brain cells.

Schlossmacher's team wants to test whether feeding rapamycin and other approved drugs to mice with Parkinson's-like symptoms also lowers the amount of alpha-synuclein in brain cells, just as introducing more GBA1 did. "If we were successful with exploiting this connection between GBA1 and alpha-synuclein with already approved drugs," he says, "we could potentially make a difference (in Parkinson's disease)."

In the meantime, there is no cure for Parkinson's—only treatment to control symptoms. "It's not good enough anymore to improve a little bit of memory function or a little bit of tremor through therapy," he says. "What we need to do is to get to the root cause of Parkinson's. That's how we will arrest this disease."

Schlossmacher believes the relationship between GBA1 and alpha-synuclein is taking scientists closer to the fundamental cause of the disease and its ultimate treatment—the holy grail in Parkinson's research. RP

IN PARKINSON'S DISEASE

David Park has genetically engineered a mouse model to help researchers solve the puzzle of this progressive brain disorder

by Laura Eggertson

One of the biggest stumbling blocks to studying Parkinson's disease has been the lack of an animal model researchers can use to test theories on how the neurodegenerative disorder starts, how it progresses and whether it can be stopped, reversed or treated. **David Park**, a University of Ottawa professor of cellular and molecular medicine, has recently created a mouse model that will propel investigations forward into how and why dopamine-producing brain cells die, causing Parkinson's.

"Now we can study the process—that's why it's so significant," says Park, who is also assistant dean of research in the Faculty of Medicine.

Previously, the only mouse models available were exposed to toxins to produce Parkinson's-like symptoms. But researchers now know that only a small percentage of people afflicted with Parkinson's were actually subjected to toxins. Those models did not reflect the source of Parkinson's in the vast majority of people living with the disease.

Park and his team have genetically engineered mice so that they are missing a gene, DJ-1, which is linked to the familial, or inherited, form of Parkinson's disease. They then bred a line of mice with the same genetic background. Those mice have motor symptoms similar to Parkinson's and, just as in humans, they begin to show more symptoms as they age.

Researchers need to be more confident that the results they produce and the medication or other therapies they try will actually reflect what happens in humans, says Park. Since researchers cannot, of course, readily experiment on humans, they need these mouse models, he adds.

"Having an appropriate surrogate is critical in narrowing down what you think is going to be important," he says. That is especially true in testing potential targets for new or existing drugs to not only relieve symptoms, but one day cure or prevent Parkinson's.

Park uses this mouse model to investigate the brain signals that tell neurons they are damaged and should die. The death of neurons that generate dopamine, a signalling chemical in the brain, causes the motor symptoms such as stiffness and tremors that typically affect Parkinson's patients. If researchers could interrupt that signalling process, they might prevent the death of those cells.

The lack of an appropriate model is one of the reasons previous clinical trials to test potential treatments for Parkinson's may have failed, Park notes.

Now "you can test particular drugs or gene therapy interventions on the mouse models at particular stages in the (degenerative) process and figure out when they will be most effective," says Park. Having the mouse model will accelerate research into Parkinson's, saving years of trial-and-error approaches.

Pinpointing the process that results in Parkinson's disease is like assembling a complex jigsaw puzzle. "From an intellectual level, it's an incredibly difficult and convoluted puzzle that needs solving," he says. "From a patient level, you see people who suffer from Parkinson's disease and you want to help in every way you can. It's a whole range of reasons that coalesce into making me passionate about what I do."

The mice, Park believes, will finally help researchers put the jigsaw puzzle together. RP

SWEET MEMORIES

Diabetes hinders our ability to remember, no matter how old we are

by Dana Yates

Although diabetes affects many organs, the condition was once believed to leave the brain untouched. Researcher **Claude Messier** has shown, however, that diabetes impairs memory and the damage happens sooner than first thought.

A professor in the University of Ottawa's School of Psychology, Messier studies the effects of glucose on memory. His research has led to tremendous changes in the field. During the mid-1990s, at a time when many researchers thought that diabetes and Alzheimer's disease were unrelated, Messier wrote a review that explained how the former could indeed be a risk factor for the latter. Today, after further work by other scientists, it is widely accepted that insulin resistance—a hallmark of type 2 diabetes—can hasten the onset of Alzheimer's disease.

> "We used to call type 2 diabetes 'old age diabetes,' but it's now 'every age diabetes.'"
>
> – Claude Messier

Messier and his research team have found that both memory and the capacity to perform complex mental tasks are impaired in older people who are not yet diabetic, but who show early signs of the disease. But that doesn't mean that type 2 diabetes is only an illness of the elderly, he cautions.

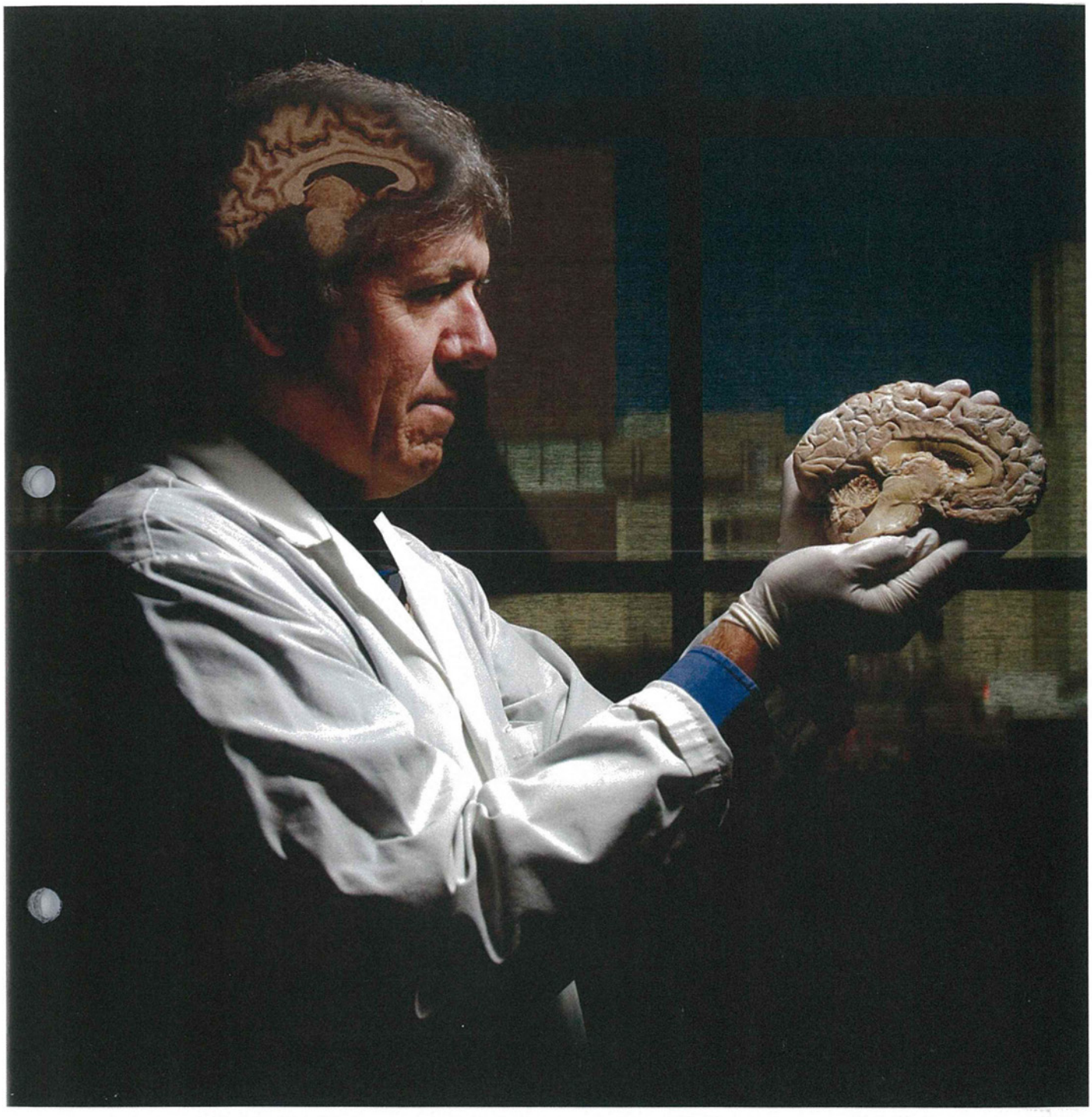
"We used to call type 2 diabetes 'old age diabetes,' but it's now 'every age diabetes,'" says Messier.

According to the Canadian Diabetes Association, more than nine million Canadians currently live with diabetes or prediabetes. With the growing prevalence of obesity and inactivity, diabetes is increasingly affecting young people. In fact, a report released earlier this year by the Centers for Disease Control and Prevention in the United States found that more than 20 percent of adolescents have diabetes or prediabetes, compared with nine percent a decade ago. Canadian research has also shown a similar increase among youth in Canada.

Unfortunately, as Messier and other researchers are discovering, being young offers no protection from the changes in intellectual functioning associated with type 2 diabetes. And those changes have a lot to do with the size of some parts of the brain. Imaging studies have shown that diabetes and its inherent high blood glucose level can lead to brain shrinkage. Even though researchers don't fully understand the mechanisms behind that reduction—cell death has been suggested—one thing is certain: when it comes to the proper functioning of the brain, decreasing size matters. Particularly since diabetes-related shrinkage occurs in areas of the brain that control the ability to make memories, learn new things, make decisions and plan ahead.

In his latest research project, Messier is looking at glucose regulation and specific cognitive changes among young non-diabetics. So far, he has found that the brain can suffer from the effects of high glucose levels long before diabetes develops. But since those problems may be mild and even undetectable by people experiencing them, those who are at risk of developing diabetes may not make the necessary lifestyle changes to help prevent the disease. Those measures include healthy eating, being physically active and controlling one's weight.

Messier admits it is difficult to convince people to change their eating and exercise habits decades before facing a diabetes diagnosis—our brains are not naturally inclined to take the long view. He, however, has seen first-hand the positive results of early and effective management



of blood glucose levels. His uncle, Bernard Messier, a former director of the Department of Anatomy at Université de Montréal (and Messier's "inspiration for doing research"), was diagnosed with diabetes in his forties. By carefully managing the condition, though, he has continued to maintain strong cognitive abilities into his late eighties.

In his early days as a researcher, Messier discovered a physiological paradox: consuming a high-glucose meal produced cognitive improvement, but only in people already struggling with insulin resistance. "Our bodies are not meant to sustain high glucose levels," he says, "be it because of diabetes or eating snacks throughout the day."

The key, says Messier, is for researchers to find a way to restore the brain's sensitivity to insulin and to protect the brain from the vascular problems that accompany diabetes. The importance of such a discovery cannot be overstated: for the earlier in life people experience consistently high blood sugar levels, the earlier they may experience attendant damage to their brains. RP

Unlocking the mysteries of Alzheimer's

Steffany Bennett leads an interdisciplinary team of researchers probing the link between metabolism of fat in the brain and the risk of developing the debilitating disease

by Tony Martins

Get her talking about her research and **Steffany Bennett**'s eyes light up with a youthful enthusiasm reflected in the terms she uses to describe projects and collaborators, including "so awesome" and "really, *really,* cool."

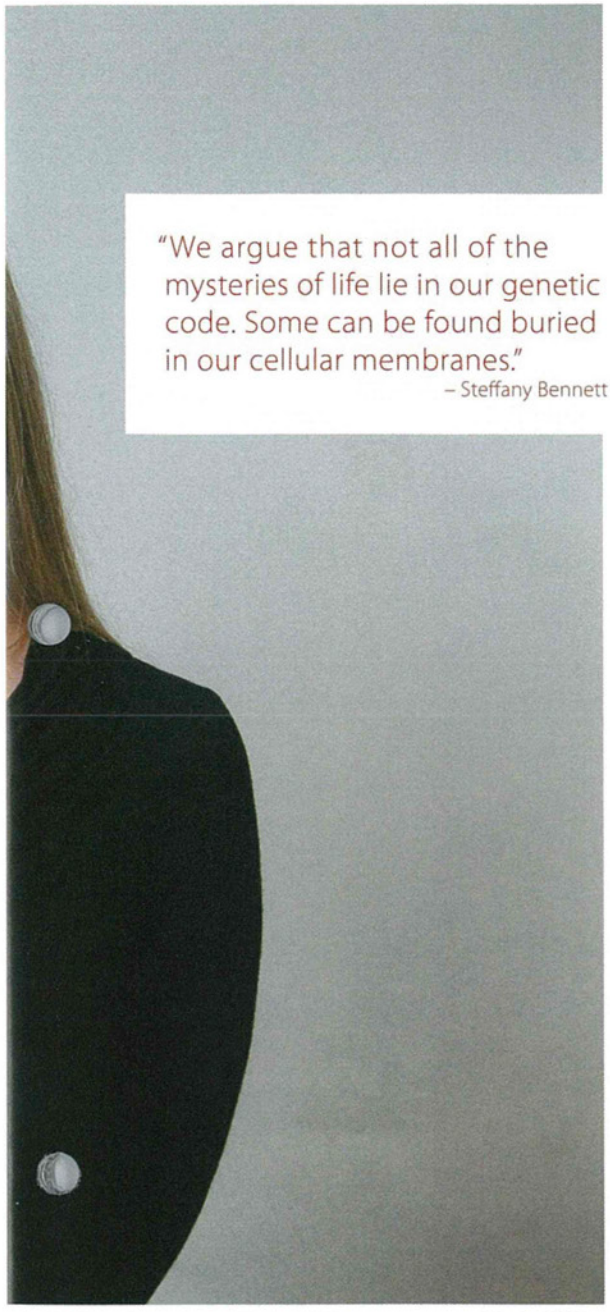
The heightened neural activity and brightness of manner that Bennett exhibits in such moments are in sharp contrast to the effects of Alzheimer's disease, the devastating and all-too-common condition that sharply erodes a sufferer's memory, personality and everyday functioning.

Alzheimer's affects some 24.3 million people in North America alone, and the most daunting aspect of the disease may be the relative scarcity of treatment options, which really only delay the inevitable.

"Alzheimer's is such an insidious disease with a slow progression, so that the brain is able to adapt and mask the symptoms for a very long period of time," says Bennett in a more sober moment. "We do not show any symptoms until a great deal of damage has already been done. Prevention and resistance are the keys to fighting this devastating disorder."

In a quest for earlier identification of Alzheimer's and to find more effective treatments, Bennett heads up two integrated research programs that together give her one of the most expansive and well-equipped networks in her field of neurodegenerative lipidomics.

Bennett's Neural Regeneration Laboratory (NRL) at the Ottawa Institute of Systems Biology is part of a rare network of laboratories located as



close to home as Carleton University and the universities of Toronto and Montréal, and as far afield as Harvard University, Nashville's Vanderbilt University and the University of Bonn in Germany.

How does Bennett continue to bring new blood into this research network?

"With the support of the Canadian Institutes of Health Research, I am very fortunate to lead a new training program in neurodegenerative lipidomics with 18 research scientists and 53 trainees at uOttawa, Carleton University, the University of Toronto and the Sunnybrook Health Centre, under the auspices of the Ottawa Institute of Systems Biology."

Though Bennett's programs integrate diverse fields, the bulk of the core research is focused on one key area: lipid metabolism, the building blocks of biological membranes.

"We argue that not all of the mysteries of life lie in our genetic code," explains Bennett. "Some can be found buried in our cellular membranes."

"The diversity of neural structural lipids, coupled with their chameleon-like capacity to shape-shift from one identity to another, allows for hundreds of immediate signalling responses," Bennett continues. "So, because each person has a different coating of brain fat at any given moment, based on our metabolism, our diet and our genetic makeup, this composition could render us susceptible or resistant to neurodegenerative disease from moment to moment."

Noting how the Alzheimer's research community has made remarkable strides in identifying potential genetic and environmental risk factors, Bennett also points out how many of these risk factors modulate lipid metabolism in the brain.

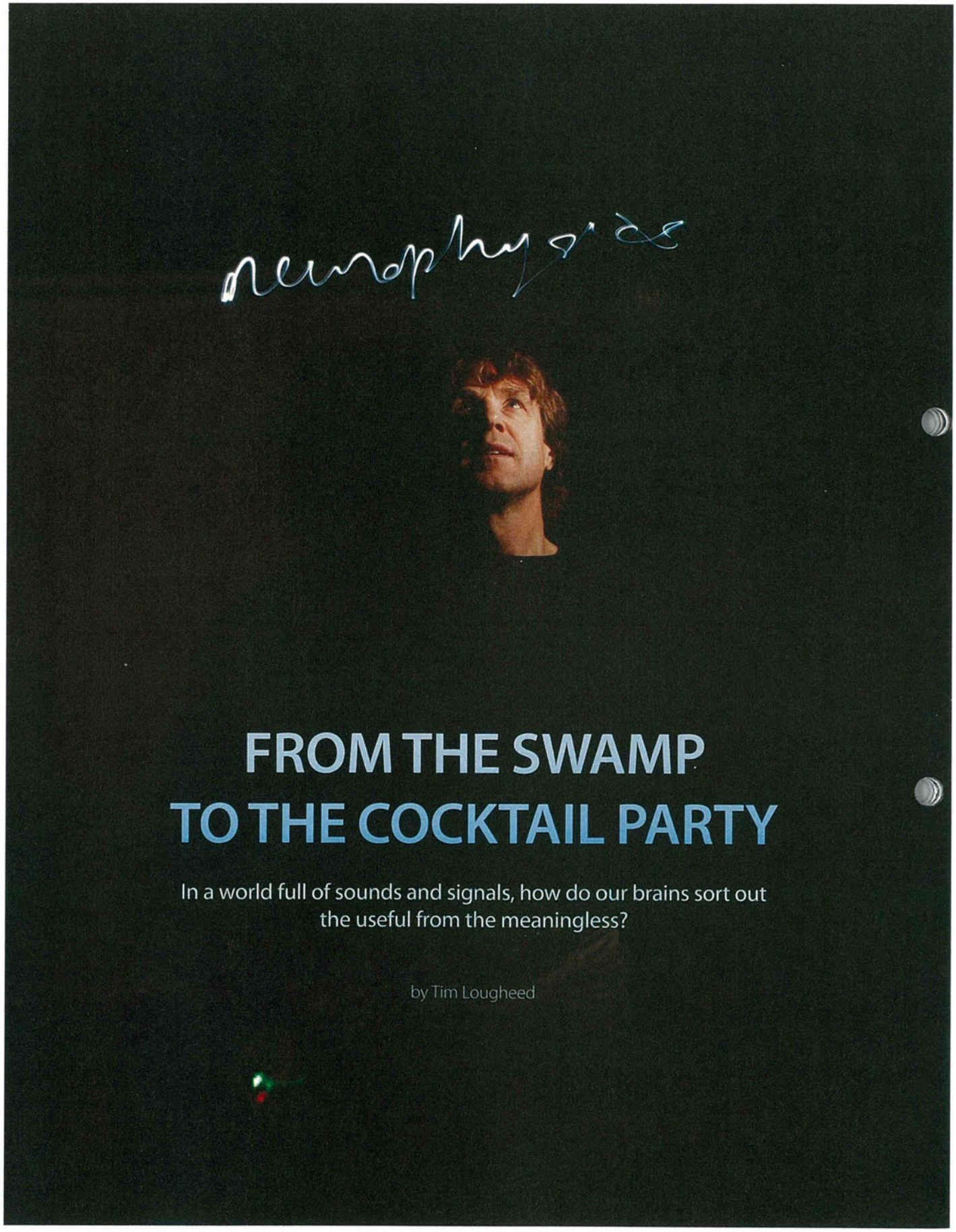
"How these small fat molecules are modified likely impacts upon our ability to resist the disease," Bennett argues. "Initially, memory dysfunction is reversible in Alzheimer's. Confused and disoriented patients can revert to being alert and coherent within minutes. This ability to return to oneself raises hope, as it suggests a metabolic component to early synaptic dysfunction that has only just begun to be explored."

Bennett's visible excitement returns when she discusses an important paper her team published in the *Proceedings of the National Academy of Science*—"one of the first to come out of our interdisciplinary team approach," she says.

The paper brings together unique expertise in cell biology, analytical chemistry, animal physiology, enzymology and medicine, examining how lipids bridge the gap between the two known pathologies of Alzheimer's.

"We are very excited by the findings that the amyloid depositions that form in Alzheimer's alter the production of a small lipid molecule called PC(O-16:0/2:0) PAF," Bennett explains. "When levels of this lipid are too high in brain cells, the lipid itself signals the cell to alter the other hallmark of Alzheimer's, the protein tau. We found that preventing the accumulation of this small lipid was sufficient to prevent these changes."

"We are excited because this work provides proof of the principle that targeted intervention in lipid metabolism has a real impact on Alzheimer's pathology. We are testing now in animals to see if this intervention can prevent the loss of memory that defines this devastating disease. This is not just the work of one person's laboratory. This is all of us working together to make a difference." RP



FROM THE SWAMP TO THE COCKTAIL PARTY

In a world full of sounds and signals, how do our brains sort out the useful from the meaningless?

by Tim Lougheed

It is among our most impressive everyday skills. Standing in a crowded room, surrounded by background music and a variety of conversations, we think nothing of being able to make sense of what the individual in front us is saying.

It is easy to take this ability for granted, but it is no less impressive than the fact that hundreds of frogs croaking in a swamp at night seem to identify one another by the frequency and number of their calls. This behaviour seems to originate from a middle portion of the brain called the torus semicircularis, which processes signals from the ears. The same structure is found in the brains of frogs and humans, as well as those of other animals whose survival depends on being able to sort out complex arrays of sound.

Physicist **André Longtin** dubs this elaborate filtering mechanism the "cocktail party algorithm." The brain function essentially sorts what is a useful signal from a meaningless, noisy or simply redundant background.

"No one knows how it works," he confesses. "We are extremely good at it. Frogs are good at it. Most animals are good at it, just to survive. But the substrate is not clear."

Longtin has spent the past three decades pondering the distinctions between noise and deterministic patterns in the brain, as well as physical systems in general. His passion began in the 1980s with mathematical models of the human auditory reflex. This work, and the technology used to explore the workings of the nervous system, have progressed significantly since then. But many of the underlying challenges have persisted.

"We've just figured out how the neuroplasticity of a fish's brain can remove redundant activity," he explains. "We and others are now also getting at the circuitry that seems to underlie voluntary action."

He notes the success of methods like functional magnetic resonance imaging, which can track brain activity in subjects as they conduct tasks such as identifying words or expressing emotions. The results are often tantalizing, and regularly accompanied by a great deal of hype suggesting brain scans can reveal such things as when we are lying. Longtin responds with one of the harsher words in the physics vocabulary: messy.

"You've got messy data, few data points, huge error bars," he argues. "We can tell which brain parts are likely engaged in a task, but we still do not know how that task is actually accomplished by cells. We don't know what the 'neural computation' is."

He adds that his own academic background builds on the research foundation laid by biology and biochemistry. "Physics and applied math can give you some of the tools to go and find the organizing measures that can tell you what's changing and predict what will happen next."

In his search for those measures, Longtin has turned to brains much simpler than ours, such as those of frogs or fish. There it should be easier to find links between the signals essential to particular functions, like communication or navigation, and the actions of particular arrangements of cells. Nevertheless, things get complicated very quickly, even as researchers move from the study of a single cell to small groups of cells.

"Nature uses resources in ways you wouldn't think are intelligent at first glance," he explains, pointing to how parts of the brain seem to handle information in much the same way computers conduct parallel processing.

In fact, the natural world could offer valuable contributions to fields such as information technology. If we learn how frogs have solved their signal processing problems in the swamp, for example, engineers may be able to refine the challenges they face on computer networks.

"We can tell which brain parts are likely engaged in a task, but we still do not know how that task is actually accomplished by cells."
– André Longtin

To find answers to such complicated questions, Longtin points to the need to strike up enduring interdisciplinary partnerships. After an extensive collaboration, Longtin and Leonard Maler, a professor in the Department of Cellular and Molecular Medicine, founded the University's Centre for Neural Dynamics in 2004. This virtual organization has built bridges between investigators in areas ranging from psychology and mathematics to systems biology and surgery.

More recently, Longtin has been working with Georg Northoff, a psychiatrist at the Royal Ottawa Hospital who studies how individuals react when their mind is unfocused and wandering, and the brain might be assumed to be "resting." Under these conditions, the brain may not have to cope with the cacophony of a cocktail party, but it nevertheless remains ready to sort out a wide variety of sights and sounds.

"We're trying to figure out what is it about this resting state, with its fluctuating neural activity, that makes you sensitive to certain stimuli and not others, and how is it altered in disease," says Longtin. "There might be something worth pursuing there, from a modelling perspective, something very exciting." RP

Off the Press

Stigma Revisited

Implications of the Mark

edited by Stacey Hannem
and Chris Bruckert

This collection of studies of people who experience stigma in their daily lives—be it through discrimination, marginality or social injustice—offers a holistic perspective. While the book features first-person accounts of marginalized individuals, including a homeless man, many of its academic contributors have also personally dealt with the stigma that their subjects bear: among them is a criminologist and former sex trade worker who has devoted her career to researching the Canadian adult sex industry and advocating sex worker rights.

Stigma Revisited is inspired by Canadian sociologist Erving Goffman's seminal 1963 book *Stigma: Notes on the Management of Spoiled Identity.* It addresses the challenges that researchers studying stigma face, concluding, "in short, we are all affected by stigma as both subjects and perpetrators—indeed at times simultaneously." RP

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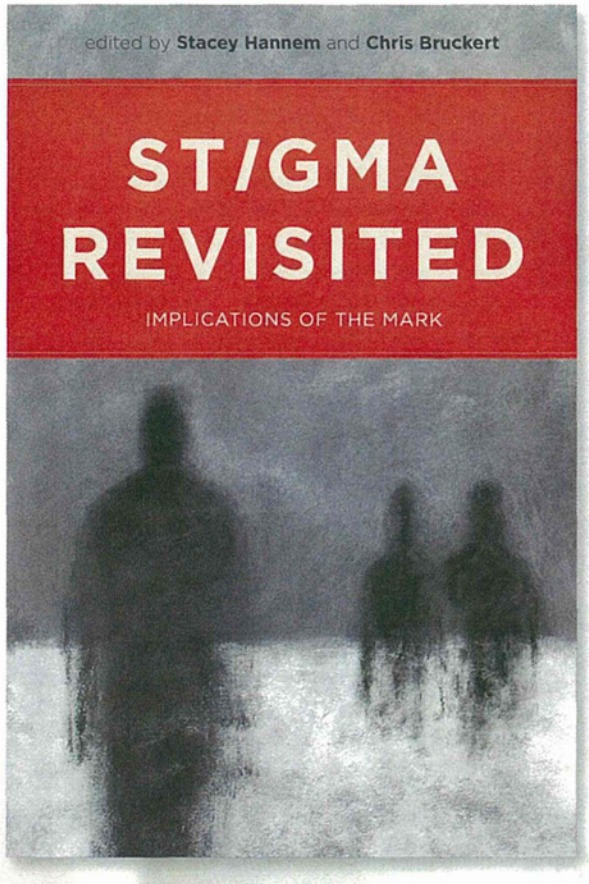

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HIDEKI HANAOKA, MD
Director of Clinical Research Center (CCRC)
Chiba University
Vice Director of Future Medicine Research Center
Department of Regulatory Science and
Public Administration of Medicine
Graduate School of Advanced Clinical Sciences

ITINERARY

February 10, 2013

TBD	Dinner Alexander/Hanaoka/Koshizaka

February 11, 2013

8:30-9:30 am NP 7023	**John Alexander** Director Cardiovascular Research
9:30-10:00 am NP 7014	**Sureh Balu**
10:00-11:00 am NP 7014	**Shelley Myles-Di Mauro** Project Leader CV Early Phase
11:00-12:00 am NP 7014	**Allison Handler** Senior Project Leader CV Industry
12:00-1:00 pm NP 3017	DCRI CV Research Faculty Meeting
1:30-2:30 pm NP 7014	**Pamela Tenaerts, MD, MBA** Executive Director Clinical Trials Transformation Initiative (CTTI)
2:30-3:30 pm NP 7023	**John Alexander** Director Cardiovascular Research

Contact: Aurea Gagliardotto
919-668-8955

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DUKE UNIVERSITY MEDICAL CENTER

HIDEKI HANAOKA, MD
Director of Clinical Research Center (CCRC)
Chiba University
Vice Director of Future Medicine Research Center
Department of Regulatory Science and
Public Administration of Medicine
Graduate School of Advanced Clinical Sciences

ITINERARY

February 11, 2013 (continue)

3:30-4:00 pm **Duk-Woo Park, Hyun-Jae Kang**
NP 7014 Research Fellow from
Korea

5:15-5:45 pm **Renato Lopes**
NP 7045 Adjunct Assistant
Professor

臨床試験部セミナー

ＡＲＯ構築と発展について

講師：John H. Alexander, MD, MHS, FACC
／Co-Director, CV Research
Duke Clinical Research Institute

開催日：２０１３年３月１５日（金）
時　間：９：００～１０：００（1時間）
会　場：イノベーションプラザ1階
セミナールーム

問い合わせ先：千葉大学医学部附属病院　臨床試験部
電話　043-226-2737（内線6959）

臨床試験に参加する患者の看護①

選択研修29

日時：2012年10月29日（月）
17:30～19:00

場所：第3講堂

講師：花岡英紀先生（臨床試験部）
田邉信宏先生（呼吸器内科）

内容：大学病院の役割と臨床試験
難病の診療と臨床試験

お問い合わせ：荒屋敷（PHS：71815）

選択研修29

臨床試験に参加する患者の看護②

日時：2012年11月26日（月）
17:30～19:00

場所：　第2講堂

講師：荒屋敷亮子看護師長（臨床試験部）
金子洋子副看護師長（臨床試験部）

内容：臨床試験に参加する患者の看護
臨床試験における看護師の役割

お問い合わせ：荒屋敷（PHS：71815）

平成24年度看護部研修　臨床試験を受ける患者の看護

2012.10.29

大学病院の役割と臨床試験

どのようにしたら治験と臨床試験の科学性と倫理性を確保できるのか？

臨床試験部
花岡英紀

1. 臨床試験の倫理
2. 臨床試験の種類
3. 国際共同試験
4. 千葉大学の取り組み

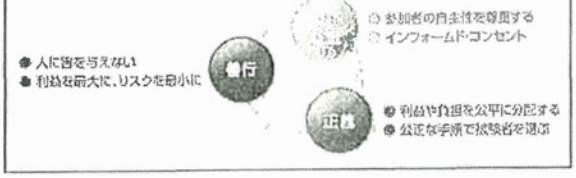
1　臨床試験の倫理

倫理的立場からの問題点

- 対象者をアフリカの貧困層としていること
- 十分な説明がないこと
- 死亡という結果に至っていること
- 開発した医薬品は欧米で使用されること

ベルモント原則に当てはめると

- 人格の尊重・・・本人の自己決定権
- 善行・・・・人を傷つけてはならない
- 公正・・・・研究への利益や負担を公平に分配しなければならない



人格の尊厳

- 個人は自律的な主体として扱われるべきである
- 自律性の弱くなっている個人は保護を受ける権利がある
- つまり人間の自律性を認めること、弱くなっている自律性を保護すること

善行

- 害をなしてはならない
- 利益をできるだけ大きくし、害をできるだけ小さくする
- 一人の人間を傷つける行為はそれが他の人々に利益をもたらすことがあっても行ってはならない
  - しかし、害をさけるということにおいてさえ何が害になるのかを学ばなければならないそのための情報を得られる過程で人は害を受ける危険にさらされるかもしれない

公正(正義)

- 分配の公平性
- ある種の人々が利用しやすさ、立場の弱さ、扱いやすさなどの理由だけから系統的に被験者に選択をされていることはないかということを吟味する必要がある
- 研究によって得られる利益に預かれない人たちを不当に被験者として参加させることはあってはならない

第二次世界大戦後の研究倫理綱領

- 1947 ニュルンベルクコード
- 1964 ヘルシンキ宣言
- 1979 ベルモント・レポート
- 1981 コモン・ルール45CFR46
- 1993 CIOMSによる倫理ガイドライン
- 1996 ICH-GCP

臨床試験と死亡事故

Healthy volunteer death 2001.6.2

2800の臨床試験の中止およびプロトコールの再検討が指示された。

Research leader of Johns Hopkins

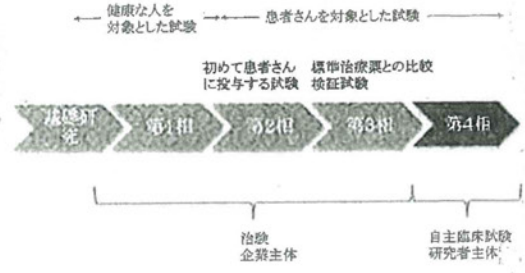
Ellen Marie Roche(24)

2 臨床試験の種類

治験と臨床試験

- 治験
  - 薬事法・GCP
  - 製薬企業が承認申請を厚生労働大臣に行う
  - 数億から数十億の費用を要する
- 臨床研究（自主臨床試験）
  - 臨床研究に関する倫理指針
  - 治験以外の臨床試験を意味する
  - 新しい治療方法の確立を目指す
- 疫学研究
  - 疫学研究に関する倫理指針

試験の段階



最近の喘息治療薬

- サルメテロール
- ザフィルルカスト
- フルチカゾン
- モンテルカスト
- ベクロメタゾン
- シクレソニド
- サルメテロール・フルチカゾン
- オマリズマブ

モンテルカスト（小児）

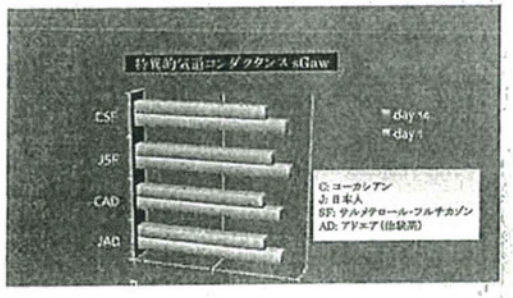
1-6歳未満 4mg

- Phase 2 open study (2-6 year) n=45, 4 weeks
- Phase 2 study (1 year) n=16, 4 weeks
- Phase 2 study (1-6year) n=67, 8 weeks
- 発作回数の変化量
- 薬物濃度

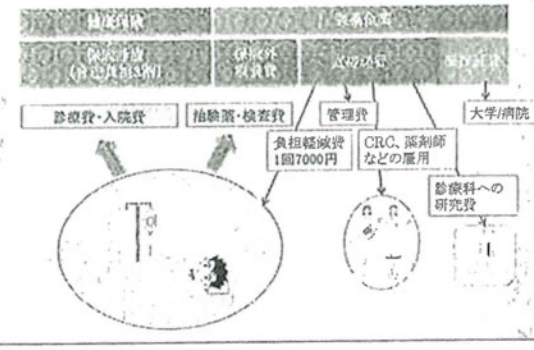
6歳以上 5mg

- Phase 3 double blind study n=180, 4 weeks (ケトチフェン対照)
- Phase 3 double blind study n=80, 4 weeks (ベクロメタゾン、フルチカゾン併用テオフィリン対照)
- Primary end point= Δ PEF, 2 weeks

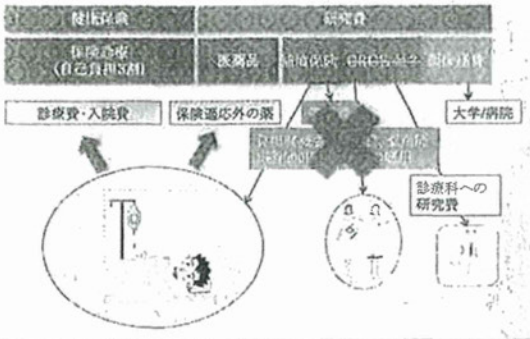
サルメテロール・フルチカゾン



治験の医療費はどこから支払われる？



自主臨床試験の医療費は？



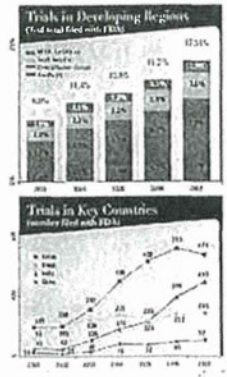
一緒に考えて欲しいこと

- 臨床試験に関わる人材の育成が重要である
- すべてのスタッフに臨床試験の知識が必要である
- 臨床試験は大学病院の使命である
- 新しい治療方法の発信
- 目の前の患者さんを助けること
- どのような治療が行われているのか、副作用はなにか？知る必要がある

3 国際共同試験

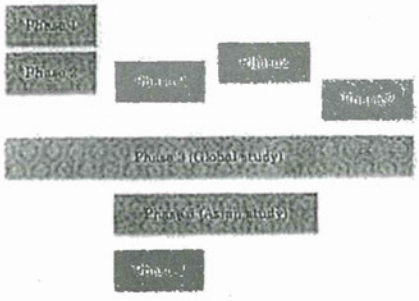
私たちも世界の一員です

国際共同治験推進と騒いでいるが、欧米企業の臨床試験の実施場所は東欧、ロシア、南米、インド、中国へ



Science 322: 210-223, 2008 (Oct 10)

国際共同試験



新薬開発における海外AROの試験実施体制（例）

UK, North America, China, Germany, Italy, Scandinavia

PIによるSteering committeeと世界のAROの連