



Society of
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Newsletter

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News from the SMR

David E. Fisher (President of SMR)

Dear SMR members:

We've had an exciting Fall season. The Melanoma Congress in New York City was not only a major success for the outstanding attendance and quantity of science which was presented. It was also continuously buzzing with excitement and anticipation. Our field is moving... and the movement is very exciting! Investigators are moving to the melanoma field because it offers such an attractive system in which to apply their technologies. Pharma is increasingly attracted to melanoma for clinical trials because of the elucidation of pathways that are mutated in the disease. From biology of the skin to biology of the metastatic solid tumor, melanoma is being vigorously attacked, and the secrets are increasingly being revealed. Membership in SMR has risen dramatically, due to the tireless efforts of individuals on the Membership Committee. Please continue to spread the word about SMR- membership is affordable, and provides access to the premier society in the melanoma field. The 2008 Congress is coming up next May, and we'll await announcements from Kowichi Jimbow regarding specifics for registration. The program is shaping up to be another spectacular event for the field.

A number of additional initiatives are underway at SMR, including updating the Melanoma Roadmap towards a cure, working with NCI-Congress and advocates to push for additional melanoma research funding, and planning of future congresses. The 2009 Congress will be held in Boston, chaired by Steve Hodi, Jeff Sosman, and myself.

Hoping the Red Sox will be on an uninterrupted run at that time (sorry to Steve Hodi and our New York friends who are Yankee addicts).

Best wishes for the upcoming New Year, and ever more exciting and important discoveries in our field!

David

David E. Fisher MD, PhD
President
Society for Melanoma Research

Recent development in melanoma research (review on literature)

Research highlights (Meenhard Herlyn)

Coming down the pipeline

Many of the SMR members attended an outstanding, science-filled congress in November in New York. I hear from Ze'ev Ronai that there will be a report in our PCMR journal in the near future. Thus, I will not report on the exciting new findings coming from the meeting but will comment on emerging technologies.

New technologies will dictate many aspects of future progress in research, including in melanoma research. Does the single investigator struggling to stay afloat need to jump on every new technology train that is praised as the solution for the next breakthroughs? Hardly. Is Nanotechnology a bust, because it was over-hyped by those who had a vested interest in it or who were in the position to single-handedly promote the virtues of the technology? Were several hundred million spent by the NIH/NCI in vain? Likely, we learned something from the technology in the next few years and the few remaining people who continue in this field are still optimistic that it will bring major breakthroughs in both cancer diagnostics and therapeutics. But nanotechnology in all likelihood was promoted too fast to involve the general scientific population. When attending an NIH meeting just four years ago, I seriously felt the need to jump on this train to not jeopardize the next grant renewals. Luckily, I never got beyond reading a few reviews and I gladly stay on the sidelines until the experts have sorted out what is feasible.

Other new technologies quickly conquered the world of biomedical science. The most dramatic in recent years was the siRNA technology that came originally out of the fly field and for many years struggled to also work to mammalian cells. Today most experimental labs use RNAi technologies, which have become indispensable tools to 'knock-down' gene expression in cells. There is still some magic to make it work and it is generally accepted that you test five sequences and then at least one will work. siRNA libraries representing most genes in the genome are now available in many major research centers to perform large-scale screening studies. There is always the danger that you also hit innocent bystander genes but the specificity and efficacy using siRNA is just remarkable. What are good vectors for delivering siRNA? When I heard Inder Verma from Salk Institute first speak ~10 years ago about HIV viruses as vectors carrying a gene load, I thought he was crazy because from the adenoviral vectors we knew

of relatively frequent recombination events leading to an infectious virus. In HIV, this would be unacceptable. I followed the progress of this new vector generation for some time from the distance until I finally forgot about it. Then suddenly there was a new storm of excitement when lentiviruses were described as vectors for gene delivery. These were the descendants of the HIV viruses that Inder Verma had worked on. In the new vectors, the original virus was further crippled but it had several major advantages from the standard retroviruses: You can infect any cell, not just few permissive cell types, because it now acts like a vesicular stomatitis virus (VSV), which has a very broad infectivity range. Lentiviruses also infect cells that do not proliferate. Unlike the 'old' retroviruses, producing infectious lentiviral particles in a workhorse cell line is not too difficult and relatively high titers can be reached, which was a real drag for the retroviruses. Lentiviruses have widely replaced the adenoviral vectors because they induce stable integration of the transferred sequences into cells. They became the vector of choice for siRNA, now labeled shRNA (single hairpin RNA). shRNA libraries of most genes are today available for those who can afford them. Many institutions have special deals with Sigma, one of the distributors for shRNA and we can purchase the four or five vectors per gene for \$195, which is way cheaper than constructing them ourselves, a task that takes even an experienced person several weeks. To my knowledge, lentiviruses have not yet made it into patients for gene therapy but at least some retroviruses have. Adenoviruses have become discredited as vectors of choice for gene therapy, a field that was widely hyped, then damned and that now makes a quiet but steady comeback. Will RNAi technology make it into the clinics for therapy? At least few small biotechnology companies think so but it will take some time. Here is a problem: the general scientific public will hardly touch the technology because it is tightly protected with patents. Time will tell whether anything will emerge from the current shroud of secrecy. This is unfortunate because siRNA conquered the science world because of open distribution policies.

Which other technologies that started with great promise have had difficulties to deliver? Proteomics? My colleague David Speicher from our institution just convinced me to commit to a series of protein sequencing experiments. I agreed but not as enthusiastic as several years ago, when proteomics was the craze for all in cancer and was labeled the future. One argument convinced me, which came from a grant reviewer: How do you know that your microarray experiments will provide you with expression patterns of cell surface receptors on stem cells because RNA-based assays favor those genes that have high turnover, i.e., nuclear and cytoplasmic genes? In contrast, cell surface receptors turn over only slowly and their RNA is barely found in arrays. We never think kindly of overly smart reviewers but this person had a point. The review came about six

weeks ago and in two weeks we will begin the experiment. The advances in proteomics have been phenomenal but the problems to overcome were huge mountains. For any institution proteomics labs are a real money sink because the technology is moving so rapidly that every 2 or latest 3 years new mass spectrometers are to be acquired for >1\$Million each. The problem is that those proteins most of us are interested in are present in low abundance. They are the hardest to find. The 'trick' in the most widely used sequencing approaches is to fragment all proteins, sequence the fragments, and then put the pieces of the puzzle together again through powerful computing. Thus the stumbling block is less the actual sequencing but the computational work it takes to put the pieces together to get a read-out from the cells. David, a world-class expert in this field, tells me it will take between eight weeks and six months. This sounds like forever. Still, we will obtain important information for our stem cell project and he hopes that 100,000 cells are sufficient for a read-out. I hope too.

Technologies will dictate to a large extent our progress. Jumping on every emerging train is impossible and each of us will make his/her own decision, when to jump or even get involved in the very beginning. Once the train has gathered full speed, an information flood is expected but the train will be crowded and finding our niche will be more difficult.

Melanocytes, nevi and melanoma - a literature survey (Dorothy Bennett)

This is mostly a simple list from which people can follow up their own interests, from literature in the last 6 months. A few stem-cell-related papers have been included, and a few comments [in brackets].

Barker N, van Es JH, Kuipers J, Kujala P, van den Born M, Cozijnsen M, Haegebarth A, Korving J, Begthel H, Peters PJ, Clevers H. **Identification of stem cells in small intestine and colon by marker gene Lgr5.** Nature. 2007 Oct 25;449(7165):1003-7. Epub 2007 Oct 14.
[A possible pan-stem-cell marker.]

Bataille V, Kato BS, Falchi M, Gardner J, Kimura M, Lens M, Perks U, Valdes AM, Bennett DC, Aviv A, Spector TD. **Nevus size and number are associated with telomere length and represent potential markers of a decreased senescence in vivo.** Cancer Epidemiol Biomarkers Prev. 2007 Jul;16(7):1499-502.
[An indication that telomere shortening may contribute to the senescence in nevi.]

Brychtova S, Fiuraskova M, Hlobilková A, Brychta T, Hirnak J. **Nestin expression in cutaneous melanomas and melanocytic nevi.** J Cutan Pathol. 2007 May;34(5):370-5.
[Nestin is a neural crest stem-cell marker.]

Ha L, Ichikawa T, Anver M, Dickins R, Lowe S, Sharpless NE, Krimpenfort P, Depinho RA, Bennett DC, Sviderskaya EV, Merlino G. **ARF functions as a melanoma tumor suppressor by**

inducing p53-independent senescence. Proc Natl Acad Sci U S A. 2007 Jun 26;104(26):10968-73. Epub 2007 Jun 19.

Hoek KS. **DNA microarray analyses of melanoma gene expression: a decade in the mines.** Pigment Cell Res. 2007 Dec;20(6):466-84.

[Review, and how not to do gene-expression profiling.]

Johansson P, Pavey S, Hayward N. **Confirmation of a BRAF mutation-associated gene expression signature in melanoma.** Pigment Cell Res. 2007 Jun;20(3):216-21.

Jones R, Ruas M, Gregory F, Moulin S, Delia D, Manoukian S, Rowe J, Brookes S, Peters G. **A CDKN2A mutation in familial melanoma that abrogates binding of p16INK4a to CDK4 but not CDK6.** Cancer Res. 2007 Oct 1;67(19):9134-41.

Krimpenfort P, Ijpenberg A, Song JY, van der Valk M, Nawijn M, Zevenhoven J, Berns A. **p15Ink4b is a critical tumour suppressor in the absence of p16Ink4a.** Nature. 2007 Aug 23;448(7156):943-6.

[Another senescence mediator that may be relevant to nevi.]

Mihic-Probst D, Kuster A, Kilgus S, Bode-Lesniewska B, Ingold-Heppner B, Leung C, Storz M, Seifert B, Marino S, Schraml P, Dummer R, Moch H. **Consistent expression of the stem cell renewal factor BMI-1 in primary and metastatic melanoma.** Int J Cancer. 2007 Oct 15;121(8):1764-70.

Ortiz P, Vanaclocha F, López-Bran E, Esquivias JI, López-Estebarez JL, Martín-González M, Arrue I, García-Romero D, Ochoa C, González-Perez A, Ruiz A, Real LM. **Genetic analysis of the GRM1 gene in human melanoma susceptibility.** Eur J Hum Genet. 2007 Nov;15(11):1176-82. Epub 2007 Jul 4.

Rákossy Z, Vízkeleti L, Ecsedi S, Vokó Z, Bégány A, Barok M, Krekk Z, Gallai M, Szentirmay Z, Adány R, Balázs M. **EGFR gene copy number alterations in primary cutaneous malignant melanomas are associated with poor prognosis.** Int J Cancer. 2007 Oct 15;121(8):1729-37

Ryu B, Kim DS, DeLuca AM, Healey MA, Dunlap S, Fackler MJ, Herman J, Alani RM. **Id1 expression is transcriptionally regulated in radial growth phase melanomas.** Int J Cancer. 2007 Oct 15;121(8):1705-9.

[ID1 is a suppressor of p16 expression.]

Wang Y, Dai DL, Martinka M, Li G. **Prognostic significance of nuclear ING3 expression in human cutaneous melanoma.** Clin Cancer Res. 2007 Jul 15;13(14):4111-6.

Wang YF, Jiang CC, Kiejda KA, Gillespie S, Zhang XD, Hersey P. **Apoptosis induction in human melanoma cells by inhibition of MEK is caspase-independent and mediated by the Bcl-2 family members PUMA, Bim, and Mcl-1.** Clin Cancer Res. 2007 Aug 15;13(16):4934-42. Epub 2007 Jul 25

Yang G, Curley D, Bosenberg MW, Tsao H. **Loss of xeroderma pigmentosum C (Xpc) enhances melanoma photocarcinogenesis in Ink4a-Arf-deficient mice.** Cancer Res. 2007 Jun 15;67(12):5649-57.

Meeting report

Report on the 4th International Melanoma Congress

The 4th International Melanoma Congress was held from November 1-4, 2007, in New York City. Everyone seemed to agree that it was a big success - although a bit crowded. Interest in attending the meeting was high, but we were limited to 500 and did actually have 515 registrants from 39 countries. There was a strong attendance from post-doctoral fellows and junior faculty which is wonderful for the melanoma community. Most of the sessions were plenary, allowing all to attend. Generous sponsors who helped to make the meeting a success were Bristol-Myers, Onyx, Pfizer, Schering-Plough, Astra Zeneca, Progen and Synta. Boris Bastian was the Keynote Speaker on the opening evening. The themes that ran through the Congress were focused on each stage of melanoma and the major questions asked: "why melanocytes develop into melanoma", "why are melanomas so metastatic", "why melanomas don't die", "what went wrong in the wiring of melanoma" and "where are we headed - promising models and pathways and evolving therapies". Minisymposia covered Immunobiology, Gene Expression and microRNA, Epidemiology and Prevention and Clinical Updates. The presidency of the Society for Melanoma Research was handed off from Meenhard Herlyn, the founder of the Society, to David Fisher (photo below).



Upcoming meetings

Vth International Melanoma Research Congress, May 7 - 12, 2008

<http://www.e-convention.org/ipcc-imrc2008/>

Abstract deadline: January 15th

There are Travel Awards available!

For members



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Mohamed L Salem, Mark P Rubinstein, David J Cole

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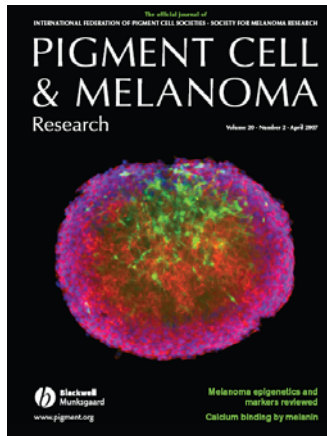
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